UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

FERRING PHARMACEUTICALS INC., FERRING B.V., and FERRING INTERNATIONAL CENTER S.A., Plaintiffs, v. SERENITY PHARMACEUTICALS, LLC, and REPRISE BIOPHARMACEUTICS, LLC, Defendants.	Case No. 1:17-cv-09922 (CM) (SDA)
SERENITY PHARMACEUTICALS, LLC, REPRISE BIOPHARMACEUTICS, LLC, and AVADEL SPECIALTY PHARMACEUTICALS, LLC, Counterclaim-Plaintiffs, v. FERRING B.V., FERRING INTERNATIONAL CENTER S.A., and FERRING PHARMACEUTICALS INC., Counterclaim-Defendants.	Case No. 1:17-cv-09922 (CM) (SDA)

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TABLE OF ABBREVIATIONS

Abbreviation	Term
'074 application	United States Patent Application Number 12/173,074
'100 application	United States Patent Application Number 10/706,100
'203 patent	United States Patent Number 7,405,203
2007 Reprise Serenity Agreement	License Agreement between Reprise and Serenity dated March 1, 2007
'302 patent	United States Patent Number 9,539,302
'321 patent	United States Patent Number 7,579,321
'615 application	United States Patent Application Number 11/744,615
'761 patent	United States Patent Number 7,799,761
2008 CPEX-Serenity Agreement	Development and License Agreement between Bentley Pharmaceuticals, Inc. and Serenity, dated February 4, 2008
2009 Amendment to the 2007 Reprise Serenity Agreement	Amendment to the License Agreement between Reprise and Serenity, dated November 4, 2009
2010 Reprise Assignment to Allergan	Agreement between Repise, Serenity, Allergan Sales, LLC and Allergan, Inc. entered into as of March 31, 2010
2010 Serenity-Allergan LTDA	License, Transfer, and Development Agreement by and among Serenity and Allergan Sales, LLC, Allergan USA, Inc., and Allergan, Inc., entered into as of March 31, 2010
2012 action	*Ferring B.V. et al. v. Allergan, Inc., et al.*, C.A. No. 1:12–cv-2650 (PKC) (S.D.N.Y.)
2017 Avadel License Agreement	Exclusive License and Assignments Agreement between Serenity and Avadel, made as of September 1, 2017
2017 Reprise Serenity Agreement	License Agreement between Reprise and Serenity made July 7, 2017 and made effective as of May 28, 2017
asserted claims	claims 6, 10, 11, 12, and 13 of the '203 patent and claims 3, 5, 6, 7, and 12 of the '321 patent
Avadel	Avadel Specialty Pharmaceuticals, LLC
Berl Declaration	Declaration of Tomas Berl, MD, under 37 CFR § 1.132, dated January 3, 2008
Broad Agreements	The 2010 Serenity-Allergan LTD and the 2017 Avadel License

Abbreviation	Term
	Agreement
CDI	central diabetes insipidus
CFR	Code of Federal Regulations
C_{max}	the maximum plasma concentration achieved after administration of a drug to a subject
Combined Declaration	Combined Declaration and Power of Attorney for Sole Inventor signed by Seymour Fein and dated March 19, 2004
common specification	specification of the '203 patent and the '321 patent, which is common to both patents
Counterclaimants	Serenity and Reprise
CV	coefficient of variation
Divis First Day Declaration	Declaration of Gregory J. Divis in Support of the Debtor's Chapter 11 Petition and Requests for First Day Relief, D.I. 10, filed in Case 19-10248-CSS (D. Del. Banruptcy Court February 6, 2019).
EC_{50}	the plasma concentration of a drug that produces 50% of the maximum pharmacodynamic effect
ELAA	2017 Avadel License Agreement
EPO	European Patent Office
Eur '821 patent	European Patent Number 2442821
FDA	United States Food and Drug Administration
Ferring	FPI, Ferring B.V., and FICSA
Ferring 1998 label	the 1998 package insert for Ferring's DDAVP tablets
Ferring-Cardinal Agreement	License and Supply Agreement between Cardinal Health UK and FICSA, effective July 13, 2005
Ferring patents	United States Patent Number 7,560,429 and United States Patent Number 7,947,654
FICSA	Ferring International Center S.A.
Finnish 2001 label	the Summary of Product Characteristics for Ferring's MINIRIN 0.1 mg tablet
Fjellestad-Paulsen (1993)	Fjellestad-Paulsen, A. et al., "Pharmacokinetics of 1-deamino-8-D-arginine vasopressin after various routes of administration," 38 CLIN. ENDOCRINOLOGY 177-182 (1993)

Abbreviation	Term
FPI	Ferring Pharmaceuticals Inc.
GB application	Great Britain Patent Application Number GB0210397.6
i.v.	intravenous
MEC	the "minimum effective concentration" of a drug
MPEP	Manual of Patent Examining Procedure
MTC	the "minimum toxic concentration" of a drug
NOCTIVA NDA	New Drug Application Number 201656
Opp'n Response	Response to Notice of Opposition submitted to the EPO on behalf of Serenity on August 7, 2018
patents in suit	the '203 patent and the '321 patent
PCT '463	PCT Application Number PCT/US2003/014463
PNE	primary nocturnal enuresis (bedwetting in children)
POSITA	person of ordinary skill in the art
PTO	United States Patent and Trademark Office
Relevant Agreements	the 2007 Serenity Reprise Agreement, the 2009 Amendment to the 2007 Reprise Serenity Agreement, the 2010 Reprise Assignment to Allergan, and the 2017 Reprise-Serenity Agreement
Reprise	Reprise Biopharmaceutics, LLC
Serenity	Serenity Pharmaceuticals, LLC
$T_{1/2}$	the half-life of a drug
T_{max}	the duration of time it takes to reach C_{max}
transmucosal limitations	"transmucosal," "transmucosal delivery" / "transmucosal . . . delivery," "delivering to the bloodstream . . . by [via] transmucosal . . . administration," and "transmucosal administration" / "administering . . . by transmucosal administration"
Yamaguchi 2012	Yamaguchi, O. et al., *Gender difference in efficacy and dose response in Japanese patients with nocturia treated with four different doses of desmopressin orally disintegrating tablet in a randomized, placebo-controlled trial*, 111 BJU INT. 474, 484 (2012)

Pursuant to the Court's October 7, 2019 Memo Endorsement (D.I. 555), Plaintiffs Ferring Pharmaceuticals Inc. ("FPI"), Ferring B.V., and Ferring International Center S.A. ("FICSA"), (collectively, "Ferring") submit the following proposed findings of fact and conclusions of law regarding Ferring's claims and defenses in the above-referenced action against Serenity Pharmaceuticals, LLC ("Serenity") and Reprise Biopharmaceutics, LLC ("Reprise") (collectively, "Counterclaimants"). Specifically, these proposed findings of fact and conclusions of law pertain to the following claims and defenses:

- Invalidity of claims 6, 10, 11, 12, and 13 of United States Patent Number 7,405,203 and claims 3, 5, 6, 7, and 12 of United States Patent Number 7,579,321 under 35 U.S.C. § 112, ¶¶ 1, 2;
- Invalidity of claims 10, 11, 12, and 13 of United States Patent Number 7,405,203 for obviousness under 35 U.S.C. § 103;
- Invalidity of United States Patent Number 7,405,203 and United States Patent Number 7,579,321 under 35 U.S.C. § 102(f);
- Unenforceability of United States Patent Number 7,405,203 and United States Patent Number 7,579,321 because of inequitable conduct; and
- Noninfringement of claims 6, 10, 11, 12, and 13 of United States Patent Number 7,405,203 and claims 3, 5, 6, 7, and 12 of United States Patent Number 7,579,321 under 35 U.S.C. § 271(a)-(c);
- Damages, to the extent the patents in suit are found to be infringed, valid, and enforceable; and
- Willful infringement, enhanced damages, and attorneys' fees.

Further, pursuant to the Court's October 7, 2019 Memo Endorsement (D.I. 555), stipulated facts have been filed by the parties. (D.I. 586.)

FINDINGS OF FACT

I. Background

DFF1. There are two patents at issue in this litigation—U.S. Patent No. 7,405,203 ("the '203 patent") and U.S. Patent No. 7,579,321 ("the '321 patent") (collectively, "the patents in suit"). (*See* Stipulated Fact ¶ 21.)

DFF2. The '203 patent issued on July 29, 2008 from U.S. Patent Application 11/744,615 ("the '615 application"). (*See* Stipulated Fact ¶ 20.) The '615 application was filed by Dr. Fein, through his counsel, on May 4, 2007 as a divisional of U.S. Patent Application 10/706,100 ("the '100 application"). (JX-1-0002.) The '100 application was filed by Dr. Fein, through his counsel, on November 12, 2003, as a continuation-in-part of PCT/US2003/014463 ("PCT '463"). (*See* JX-2-0002.) PCT '463 was filed by Dr. Fein, through his counsel, on May 6, 2003 and included a claim for priority to Great Britain Patent Application No. GB0210397.6 ("the GB application"). (*See* JX-2-0002.) The GB application was filed by Ferring B.V. on May 7, 2002. (JX-3-0001.)

DFF3. The '321 patent issued on August 25, 2009, from U.S. Patent Application 12/173,074 ("the '074 application"). (*See* Stipulated Fact ¶ 19.) The '074 application was filed by Dr. Fein, through his counsel, on July 15, 2008 as a continuation the '615 application. (JX-2-0002.)

DFF4. Both patents in suit purport to claim the benefit of the filing date of Ferring's GB application (May 7, 2002). (JX-1-0002; JX-2-0002.)

DFF5. The patents in suit, on their face, list Reprise as the assignee and Seymour Fein as the sole inventor. (Stipulated Facts ¶¶ 21, 23, 25.)

DFF6. The '203 patent is directed to methods for treating certain conditions or for inducing voiding postponement by administering desmopressin to a patient to achieve certain

pharmacokinetic parameters, namely desmopressin blood plasma concentrations. (JX-1-0026 at cl. 1-15.)

DFF7. The '321 patent is directed to methods for treating certain conditions or for inducing voiding postponement by administering a certain amount of desmopressin to the bloodstream of a patient to achieve certain pharmacodynamic responses, namely an antidiuretic effect lasting for a certain period of time. (JX-2-0027 to JX-2-0028 at cl. 1-21.)

DFF8. Desmopressin is a synthetic analog of the hormone arginine vasopressin, which is produced by the posterior pituitary gland and regulates the body's retention of water. (Stipulated Fact ¶ 1.) Desmopressin is used to treat conditions such as central diabetes insipidus ("CDI") (a specific type of diabetes where patients produce a lot of urine), primary nocturnal enuresis ("PNE") (bedwetting in children), and nocturia (disruption of nighttime sleep in elderly persons due to the need to urinate), which require different durations of action. (*See also* JX-1-0013 at 1:29-33.) One potentially adverse effect of desmopressin treatment is a condition called hyponatremia, which is an abnormally low concentration of sodium in the blood. (JX-1-0020 at 16:29-33.) Desmopressin formulations exhibit high inter- and intra- subject variability with respect to pharmacologic parameters. [Anticipated testimony of Dr. Nørgaard, Dr. Spaans.]

A. The parties

1. Ferring

DFF9. Ferring Pharmaceuticals Inc. is a privately-held Delaware corporation with its principal place of business located in Parsippany, New Jersey. Ferring Pharmaceuticals Inc. is owned by Ferring Holding, Inc., which is owned by Ferring B.V. Ferring B.V. is a Dutch private company headquartered in the Netherlands. Ferring International Center S.A. is a Swiss private company with its principal place of business in Saint-Prex, Switzerland. (D.I. 18 at ¶¶ 1-3.)

DFF10. Ferring has been working with desmopressin for over 45 years. Ferring did the first study with desmopressin in central diabetes insipidus ("CDI") (a specific type of diabetes where patients produce excessive amounts of urine) in 1971 and Ferring received approval in Denmark in 1972. Later on, Ferring got approval for another indication, primary nocturnal enuresis ("PNE") (bedwetting in children) and then nocturia (disruption of nighttime sleep due to the need to urinate in adults and, in particular, in the elderly). Ferring has marketed desmopressin as a nasal spray, injectable solution, oral tablet, and as an orodispersible tablet. [Anticipated testimony of Dr. Juul]

2. Serenity

DFF11. Serenity was formed in 2006 by Samuel Hershkowitz and Alain Kodsi. Dr. Fein was involved with Serenity from its inception. He was a consulting chief medical officer for Serenity and served as a director of Serenity from 2007 until sometime in early 2010. [Anticipated testimony of Dr. Hershkowitz, Dr. Fein.]

3. Reprise

DFF12. Reprise was formed in 2007. Dr. Fein formed Reprise to hold intellectual property for which he had an alleged inventorship claim. Dr. Fein and Dr. Nardi are principals and equity partners in Reprise; Linda and Maria Cheng are also partners in Reprise. Dr. Fein and Dr. Nardi are both equity stakeholders of Reprise and Serenity. Through Dr. Fein's formation of Reprise, Dr. Fein has a 44% ownership of Reprise, and he gave Dr. Nardi an 18% interest in Reprise as his business partner. Reprise, in turn, holds a 10-11% ownership stake in Serenity. [Anticipated testimony of Dr. Nardi, Dr. Fein.]

B. The parties' litigation history

1. The 2012 action

DFF13. Ferring, Serenity, Reprise, and Allergan have an extensive history of litigation with each other in both the United States and Europe related to patents covering desmopressin. (D.I. 18, ¶ 100.) In 2012, Ferring brought an action under 35 U.S.C. § 256 to correct inventorship of the same patents in suit at issue in this litigation ("the 2012 action"). Ferring alleged that the patents improperly named Seymour Fein as the sole inventor of the '231, '302, and '761 patents and that the true inventors were Jens Peter Nørgaard and Thomas Senderovitz. (2012 action, D.I. 1.)

DFF14. Two years later, in 2014, Serenity, Reprise, and Allergan counterclaimed with their own § 256 cause of action directed to two of Ferring's patents—U.S. Patent No. 7,569,429 and U.S. Patent No. 7,947,654 (collectively, the "Ferring patents")—claiming that Dr. Fein was the sole inventor or, alternatively, a co-inventor. (2012 action, D.I. 93.)

DFF15. Ferring's claims for correction of inventorship were summarily dismissed by Judge Sweet based on equitable estoppel. (2012 action, D.I. 190.) Ferring is appealing that decision to the Federal Circuit. (*Ferring v. Allergan*, Appeal No. 2020-1098 (Fed. Cir.).)

DFF16. Judge Sweet also summarily dismissed Allergan, Serenity, and Reprise's claims that Dr. Fein was the sole inventor of Ferring's '429 and '654 patent. (2012 action, D.I. 212.)

DFF17. The 2012 Action went to trial in June 2019 on the issue of whether Dr. Fein should be added as a co-inventor to the Ferring patents, wherein Serenity and Reprise alleged that Dr. Fein had contributed to the "sublingual administration" and "low dose" aspects of certain claims. (*See* 2012 action, D.I. 453 at ¶¶ 6, 10.) In September 2019, the Court held that "Serenity and Reprise have not proven by clear and convincing evidence that [Dr.] Fein

contributed 'to the conception of the subject matter' of claims of the patents-in-suit in any matter that was not insignificant in quantity." (2012 action, D.I. 453 at ¶ 142.)

2. This action

DFF18. Ferring brought this declaratory judgment action in April 2017 against Serenity, Reprise, and Allergan seeking freedom to operate with respect to Ferring's NOCDURNA product based on the United States Food and Drug Administration's ("FDA") imminent approval of Ferring's New Drug Application for NOCDURNA. (D.I. 1, as amended by D.I. 18.)[1]

[redacted]

DFF20. In response to the amended complaint, on July 14, 2017, Serenity and Reprise filed a motion to dismiss claiming that "Ferring's product [NOCDURNA] will never be approved, much less approved any time soon." (D.I. 25; D.I. 78 at 4:2-5.)

DFF21. In September 2017, Serenity and Reprise then found a new business partner, Avadel Specialty Pharmaceuticals, LLC ("Avadel") to commercialize NOCTIVA.

[1] In the original complaint, there were three patents in suit—the '203 patent, the '321 patent, and U.S. Patent No. 7,799,761 ("the '761 patent"). The '761 patent was dismissed from this action by the Court in May 2019 on Serenity, Reprise, and Avadel's representation that they "have never alleged, and will never allege that Ferring's NOCDURNA product infringes the '761 patent." (D.I. 495.)

DFF22. In May 2018, Serenity and Reprise filed a Citizens Petitions with the FDA seeking to block the approval of NOCDURNA. Avadel also filed its own Citizen Petition attempting to block approval of NOCDURNA. [Anticipated testimony of Mr. Carter.]

DFF23. Despite Serenity, Reprise, and Avadel's attempts to block approval of NOCDURNA, on June 21, 2018, the FDA approved Ferring's NDA No. 022517. (PX-13 at FERSER0367487.)

DFF24. Upon FDA approval of NOCDURNA, Serenity and Reprise, along with Avadel, promptly counterclaimed for infringement of the patents in suit (D.I. 101) and filed a motion for a preliminary injunction seeking to block Ferring from selling NOCDURNA in the United States. (D.I. 117). The Court held a six-day hearing on the motion in October 2018 and, on November 8, 2018, the Court denied Counterclaimants' request for a preliminary injunction. (D.I. 300.) The following day—November 9, 2018—Ferring launched NOCDURNA in the United States. [Anticipated testimony of Mr. Carter.]

DFF25. NOCTIVA was launched in May 2018, approximately six months prior to NOCDURNA's launch. NOCTIVA's failed commercialization, in part, caused Avadel to file for bankruptcy on February 6, 2018. [Anticipated testimony of Mr. Carter.]

DFF26. As part of the bankruptcy, the NDA for NOCTIVA (which was owned by Avadel) was sold to a third party, Roivant, while the patent rights remained with Serenity and Reprise. As a result, NOCTIVA is no longer on the market because Serenity and Reprise no longer have a commercial partner to sell NOCTIVA and Roivant exclusively holds the NDA to sell NOCTIVA in the United States. Avadel is no longer involved in this action. [Anticipated testimony of Mr. Carter.]

DFF27. A bench trial is set to commence on March 23, 2020. Ferring seeks declaratory judgments of non-infringement and invalidity for lack of written description, lack of enablement, indefiniteness, and obviousness of the asserted claims. Ferring also has affirmative defenses that mirror its declaratory judgment claims as well as an affirmative defense of failure to name the correct inventors under 35 U.S.C. § 102(f) and unenforceability for inequitable conduct before the PTO.

C. The asserted claims

DFF28. Counterclaimants are asserting infringement of claims 6, 10, 11, 12, and 13 of the '203 patent and claims 3, 5, 6, 7, and 12 of the '321 patent (collectively, "the asserted claims"). (*See* Stipulated Fact ¶ 25.)

DFF29. The asserted claims of the '203 patent, and the unasserted independent claims from which the asserted claims depend, state:

> *1. (unasserted) A method of treating nocturia, primary nocturnal enuresis, or incontinence, or for inducing voiding postponement, said method comprising administering to a patient in need thereof a pharmaceutical composition comprising a dose of desmopressin sufficient to achieve a maximum desmopressin plasma/serum concentration no greater than 10 pg/ml and maintaining the concentration within the range of about 0.5 pg/ml and 10 pg/ml for about four to six hours.*
>
> 6. The method of claim 1, comprising administering said composition by transmucosal delivery.
>
> 10. A method for inducing an antidiuretic effect in a patient comprising the step of administering to a patient a pharmaceutical composition comprising desmopressin by transmucosal, transdermal, or intradermal delivery in an amount and for a time sufficient to establish a maximum serum/plasma desmopressin concentration no greater than 10 pg/ml.
>
> 11. The method of claim 10, wherein said patient is suffering from incontinence, primary nocturnal enuresis (PNE), or nocturia.

> 12. The method of claim 10, wherein said desmopressin pharmaceutical composition is administered in an amount and for a time sufficient to establish a serum/plasma desmopressin concentration no greater than about 5 pg/ml.
>
> 13. A method for treating a patient suffering from nocturia comprising administering to a patient a pharmaceutical composition comprising desmopressin by transmucosal, transdermal, or intradermal delivery in an amount and for a time sufficient to establish a maximum serum/plasma desmopressin concentration greater than 0.1 pg/ml and less than 10 pg/ml.

(JX-1-0026 at cl. 1, 6, 10, 11, 12, 13.)

DFF30. The asserted claims of the '321 patent, and the unasserted independent claims from which they depend, state:

> *1. (unasserted) A method for inducing voiding postponement in a patient while reducing the risk that the patient develops hyponatremia comprising delivering to the bloodstream of the patient an amount of desmopressin no more than about 2 ng/kg by intranasal, transdermal, intradermal, transmucosal, or conjunctival administration, said amount being therapeutically effective to produce an antidiuretic effect lasting for no more than between about 4 and about 6 hours.*
>
> 3. The method of claim 1 further comprising advising a patient that fluid intake should be restricted after administration.
>
> 5. The method of claim 1 comprising administering desmopressin to a patient suffering from nocturia, primary nocturnal enuresis (PNE), or incontinence.
>
> 6. The method of claim 1 wherein the method produces a plasma/serum desmopressin concentration in the patient of a maximum of no more than about 10 pg/ml.
>
> 7. The method of claim 1 wherein the method produces a plasma/serum desmopressin concentration in the patient of a maximum of no more than about 5 pg/ml.
>
> *8. (unasserted) A method for inducing voiding postponement comprising administering to a patient an amount of desmopressin sufficient to produce in the patient a urine osmolality ranging above about 300 mOsm/kg for less than about 5 hours after administration.*

> 12. The method of claim 1 or 8 comprising administering the desmopressin by transmucosal administration.

(JX-2-0027 to JX-2-0028 at cl. 1, 3, 5, 6, 7, 8, 12.)

D. The Court's claim construction

DFF31. The Court issued its Opinion and Order on claim construction on January 22, 2019. (D.I. 421.) (Stipulated Fact ¶ 30.)

DFF32. The Court stated that the parties had stipulated that the following claim term preambles are limiting and are to be given their plain and ordinary meaning by the Court:

- "a method of treating nocturia, primary nocturnal enuresis, or incontinence, or for inducing voiding postponement, said method comprising," found in claim 1 of the '203 patent;
- "a method for inducing an antidiuretic effect in a patient comprising," found in claim 10 of the '203 patent;
- "a method for treating a patient suffering from nocturia comprising," found in claim 13 of the '203 patent;
- "a method for inducing voiding postponement comprising," from claim 8 of the '321 patent; and
- "reducing the risk that the patient develops hyponatremia," from claims 1 and 19 of the '321 patent.

(D.I. 421 at 8.)

DFF33. The Court construed the preamble of claims 1 and 19 of the '321 patent ("a method for inducing voiding postponement in a patient while reducing the risk that the patient develops hyponatremia comprising") "consistent with its plain and ordinary meaning as a statement of purpose—dual purposes, really" and "requires no further construction." (D.I. 421 at 13-14.)

DFF34. The Court construed "transmucosal," appearing in claims 2, 6, 10, and 13 of the '203 patent and in claims 1, 12, and 19 of the '321 patent, as "delivering desmopressin by way of a mucosal tissue, such as the sublingual mucosa." (D.I. 421 at 17.)

DFF35. The Court construed "transmucosal delivery" or "transmucosal . . . delivery," appearing in claims 2, 6, 10 and 13 of the '203 patent as "delivering desmopressin by way of a mucosal tissue, such as the sublingual mucosa." (D.I. 421 at 19.)

DFF36. The Court construed "delivering to the bloodstream . . . by [via] transmucosal . . . administration," appearing in claims 1 and 19 of the '321 patent, as "administering desmopressin by way of a mucosal tissue, such as the sublingual mucosa." (D.I. 421 at 21.)

DFF37. The Court construed "transmucosal administration" or "administering . . . by transmucosal administration," appearing in claim 12 of the '321 patent, as "administering desmopressin by way of a mucosal tissue, such as the sublingual mucosa." (D.I. 421 at 21.)

DFF38. The Court stated that the term "a dose of desmopressin sufficient to achieve a maximum desmopressin plasma/ serum concentration no greater than 10 pg/ml," appearing in claim 1 of the '203 patent, "has a well-understood meaning to a person of ordinary skill in the art. It requires no construction." (D.I. 421 at 31.)

DFF39. The Court stated that the term "desmopressin . . . in an amount . . . sufficient to establish a maximum serum/ plasma desmopressin concentration no greater than 10 pg/ml," appearing in claim 10 of the '203 patent, "has a well-understood meaning to a person of ordinary skill in the art" and "the term requires no further construction." (D.I. 421 at 32.)

DFF40. The Court stated that the term "desmopressin pharmaceutical composition . . . in an amount . . . sufficient to establish a serum/ plasma concentration no greater than about 5

pg/ml," appearing in claim 12 of the '203 patent, "has a meaning understood to a person of ordinary skill in the art and requires no further construction." (D.I. 421 at 33.)

DFF41. The Court stated that the term "desmopressin . . . in an amount . . . sufficient to establish a maximum serum/ plasma desmopressin concentration greater than 0.1 pg/ml and less than 10 pg/ml," appearing in claim 13 of the '203 patent, "has a meaning understood to a person of ordinary skill in the art. It requires no further construction." (D.I. 421 at 33-34.)

DFF42. The Court stated that the term "delivering to the bloodstream of the patient an amount of desmopressin no more than about 2 ng/kg . . . said amount being therapeutically effective to produce an antidiuretic effect," appearing in claim 1 of the '321 patent, requires no construction except that the claim term "about 2 ng/kg" is construed as "about 2 ng/kg based on the standard 70 kg human body weight estimate." (D.I. 421 at 38.)

DFF43. The Court stated that the term "delivering to the bloodstream of the patient an amount of desmopressin no more than about 1 ng/kg," appearing in claim 2 of the '321 patent, "has a well-understood meaning to persons of ordinary skill in the art and requires no further construction" except that the claim term "about 1 ng/kg" is construed as "about 1 ng/kg based on the standard 70 kg human body weight estimate." (D.I. 421 at 38.)

DFF44. The Court stated that the term "an amount of desmopressin sufficient to produce in the patient a urine osmolality ranging above about 300 mOsm/kg," appearing in claim 8 of the '321 patent, "has a well-understood meaning to a person of ordinary skill in the art" and "requires no further construction." (D.I. 421 at 39.)

DFF45. The Court construed "about 2 ng/kg desmopressin," appearing in claims 1 and 17 of the '321 patent, as "about 2 ng/kg based on the standard 70 kg human body weight estimate." (D.I. 421 at 39.)

DFF46. With respect to the "dose" limitations above (i.e., the terms in DFF38-DFF45), the Court stated that "[n]either claim 1 of the 203 Patent, nor the other asserted claims, reference a numerical dose or dose range of desmopressin." (D.I. 421 at 23.) The Court further stated that the asserted claims do "not define a particular dose range—neither expressly nor by implication . . . ." (D.I. 421 at 28; *see also* D.I. 421 at 35 ("[T]here is no dose limitation in claim 1 of the 321 Patent and the Court finds no express intent in the Common Specification to redefine its scope to include one.").)

DFF47. Finally, the Court stated that Dr. Fein's removal of dose-specific language and the word "low" from the phrase "low dose" from his claims during prosecution indicated that he intended to claim more broadly. (D.I. 421 at 30.)

E. The common specification

DFF48. The patents in suit share a common specification. While the substance of the common specification is identical, the location of text may differ by column and line across the patents in suit. (Stipulated fact, ¶ 29.)

DFF49. The majority of the common specification is directed to an orodispersible formulation of desmopressin and methods for making such a formulation. (*See, e.g.*, JX-1-0014 to JX-1-0020 at 4:20-16:15, Examples 1-7, Comparatives Examples 1-4.)[2] These portions of the

[2] For ease of reference, Ferring cites to the '203 patent (JX-1) when referring to the common specification. The same disclosures are in the '321 patent (JX-2) at different column and line numbers.

common specification were directly copied from Ferring's GB application. (*Compare* JX-1 *with* JX-3.)

DFF50. When Dr. Fein filed PCT '463 on May 6, 2003, he added to the disclosure of Ferring's GB application; specifically, he changed the title from "Pharmaceutical Formulations" to "Pharmaceutical Compositions Including Low Dosages of Desmopressin" and added disclosures directed to low doses and low plasma levels of desmopressin. (*Compare* JX-3 *with* JX-4.)

DFF51. Dr. Fein then filed the '100 application on November 12, 2003 as a continuation-in-part application of PCT '463. (JX-1-0013 at 1:8-13.) In doing so, Dr. Fein added certain new disclosures to the common specification that were not present in PCT '463. (*Compare* JX-4 *with* DX-31.)

DFF52. The common specification (incorporating the added disclosures from PCT '463 and the continuation-in-part sections from the '100 application) states that the invention is directed to pharmaceutical compositions including low dosages of desmopressin for treatment of certain human diseases. (JX-1-0013 at 1:18-21.)

DFF53. The common specification recognizes that desmopressin was already commercially available as of its filing date, and that desmopressin "is commonly prescribed for voiding postponement, incontinence, primary nocturnal enuresis (PNE) and nocturia, among other indications, including central diabetes insipidus." (JX-1-0013 at 1:28-33.)

DFF54. The common specification recognizes that desmopressin has been administered in the art intravenously, subcutaneously, intranasally, and orally. (JX-1-0013 at 1:34-35.)

DFF55. The common specification includes a table of what is presented as "[c]urrently, approved labeling" for recommended desmopressin doses for various indications and routes of administrations. (JX-1-0013 at 1:49-65.) It states that maximum plasma concentrations of desmopressin following these recommended doses "would be approximately 20-30 pg/mL." (JX-1-0013 at 1:66-2:2.) For instance, the common specification states that "[f]or the desmopressin oral tablet with only 0.1-0.15% bioavailability, a standard dose of 200-400 mcg would . . . produce a peak plasma/plasma/serum level of 20-30 pg/mL." (JX-1-0013 at 2:2-5.) The common specification, however, states that "[l]ower dosages are preferable if the same desired effect could be produced." (JX-1-0013 at 2:19-20.)

DFF56. The common specification states that "[i]t has also been unexpectedly discovered that low doses and plasma/plasma/serum levels of desmopressin are pharmacologically active and can achieve desired therapeutic efficacy." (JX-1-0014 at 3:40-43.)

DFF57. The common specification states that the "daily dosage of desmopressin" will generally be from 0.5 or 1 µg to 1 mg per dosage form. (JX-1-0014 at 4:1-3.) It also states that "[c]omparatively lower doses (e.g., lower dosages relative to the dosages above or provided in the art) are also specifically contemplated, for example from 0.5 ng to 20,000 ng, preferably 0.05 mcg (50 ng) to 10 mcg (10,000 ng), and more preferably 0.1 mcg (100 ng) to 2000 ng." (JX-1-0014 at 4:5-9.)

DFF58. The common specification includes a new section added by Dr. Fein titled "Low Dosage Analysis and Applications." (JX-1-0020 to JX-1-0021 at 16:16-17:29.) The common specification states that:

> As indicated above, doses and plasma/plasma/serum concentrations of desmopressin from 5 to 40% of the current recommended doses and resulting plasma/plasma/serum levels are therapeutically effective and in some cases safer for certain disease conditions such

> as CDI, PNE, and additional clinical indications requiring pharmacological concentration of the urine.

(JX-1-0020 at 16:18-24.) Then, the common specification states that the invention is directed to particular plasma/plasma/serum desmopressin concentrations. (JX-1-0020 at 16:45-50.) The listed plasma concentrations range from about 0.1 pg/mL to about 10 pg/mL, and preferably from about 0.5 pg/mL to about 5.0 pg/mL. (JX-1-0020 at 16:45-50.)

DFF59. The "Low Dosage Analysis and Applications" section of the common specification goes on to state its reliance on existing art with respect to desmopressin formulations and routes of administration:

> These amounts and ranges of desmopressin *may be administered by any method known in the art*, including, without limitation, intravenous (bolus, infusion); subcutaneous (bolus, infusion, depot); intranasal; transmucosal (buccal and sublingual, e.g., orodispersible tablets, wafers, film, and effervescent formulations; conjunctival (eyedrops); rectal (suppository, enema)); transdermal (passive via patch, gel, cream, ointment or iontophoretic); or intradermal (bolus, infusion, depot) as outlined below. Additionally, pharmaceutical compositions that contain desmopressin in an amount that provide[s] the above plasma/plasma/serum desmopressin levels may be prepared by the above methods and using the above carriers, *or any other method known in the art*.

(JX-1-0020 at 16:51-64 (emphases added).)

DFF60. According to the common specification, these dose ranges "can produce appropriate antidiuretic effect when administered by various routes as in the examples below:

Route of Administration	Effective Daily Dose Range
Intravenous (bolus and infusion)	0.5 ng-2000 ng
Subcutaneous (bolus, infusion, depot)	0.5 ng-2000 ng
Intranasal	0.1 mcg-20 mcg
Transmucosal including buccal and sublingual (orodispersible tablets, wafers, film and effervescent formulations), conjunctival (eyedrops), rectal (suppository, enema)	0.1 mcg-20 mcg
Transdermal (passive via patch, gel, cream, ointment or iontophoretic)	0.05 mcg-10 mcg
Intradermal (bolus, infusion, depot)	0.05 mcg-10 mcg

(JX-1-0020 to JX-1-0021 at 16:65-17:15.) The section concludes by noting that administration of low doses of desmopressin "can be an effective treatment regimen for clinical indications" and that one may also create specific formulations that may "enhance absorption and increase [] systemic bioavailability." (JX-1-0021 at 17:16-29.)

DFF61. The Examples in the common specification include examples of three different types of desmopressin formulations: an orodispersible tablet, a conventional oral tablet, and a conventional intravenous formulation. (JX-1-0021 to JX-1-0026 at Examples.)

DFF62. Examples 1 through 7 and Comparative Examples 1 through 4 were present in Ferring's GB application. (*Compare* JX-1-0021 to JX-1-0026 at Examples 1-7, Comparative Examples 1-4 *with* JX-3-0026 to JX-3-0031 at Examples 1-7, Comparative Examples 1-4.)

DFF63. Examples 1 through 6 disclose two different orodispersible tablet formulations containing 200 µg, 400 µg, or 800 µg of desmopressin. (JX-1-0021 at Examples 1 and 4 (200 µg), JX-1-0021 at Examples 2 and 5 (400 µg), and JX-1-0021 at Examples 3 and 6 (800 µg).) Examples 1 through 6 include the same active ingredient (desmopressin) and

excipients, but the amount of excipients used in Examples 1 through 3 differs from the amount of excipients used in Examples 4 through 6. (*Compare* JX-1-0021 at Examples 1-3 *with* JX-1-0021 at Examples 4-6.)

DFF64. Comparative Example 1 discloses an intravenous desmopressin solution that was "conventionally prepared." (JX-1-0021 at Comparative Example 1.) Comparative Examples 2 and 3 disclose a conventional desmopressin oral tablet formulation containing 200 µg or 100 µg of desmopressin, respectively. (JX-1-0021 to JX-1-0022 at Comparative Examples 2 and 3.)

DFF65. Example 7 provides mean (not individual) pharmacokinetic data for the orodispersible tablets of Examples 4 through 6. (JX-1-0022 at 19:28-32) Example 7 also administered the intravenous formulation from Comparative Example 1 as a bolus dose. (JX-1-0022 at 19:28-32.) Example 7 does not report mean maximum plasma concentration ("C_{max}") data for the intravenous bolus dose and instead only reports the mean volume of distribution at steady state, mean clearance, and mean elimination half-life. (JX-1-0022 at 19:64-67.) For the orodispersible tablets from Examples 4, 5, and 6, Example 7 reports a mean C_{max} of 14.25, 30.21, and 65.25 pg/ml, respectively. (JX-1-0022 at 20:2-4.) Example 7 also does not disclose the standard deviation or coefficient of variation for these mean C_{max} values.

DFF66. The disclosure in Example 7 of the common specification is based on Ferring's clinical study designated CS004. CS004 was a clinical study designed to test the absolute bioavailability of the orodispersible tablets of Examples 4 through 6. [Anticipated testimony of Dr. Nørgaard, Dr. Juul.]

DFF67. Comparative Example 4 discloses another Ferring clinical study designed to test the bioavailability of the conventional oral tablets disclosed in Comparative Examples 2

and 3. (JX-1-0022 at Comparative Example 4.) Comparative Example 4 reports a mean C_{max} of 13.2 pg/ml and 15.0 pg/ml after an oral dose of 2x100 µg and 1x200 µg, respectively. (JX-1-0022 at 20:26-33.)

DFF68. Example 8 was not present in Ferring's GB application or in PCT '463 and was added by Dr. Fein in the '100 application. (*Compare* JX-3 *with* JX-4 and DX-31.)

DFF69. Example 8 reports the results of a clinical study that involved eight (8) healthy volunteers. These volunteers were administered escalating doses of intravenous desmopressin that was infused at a steady rate over the course of two hours. (JX-1-0022 at 20:39-44.) The subjects discussed in the clinical study in Example 8 were between 18 and 40 years old and were dosed initially with 0.5 ng/kg, then with 1.0 ng/kg, and finally with 2.0 ng/kg, with a forty-eight-hour washout period between each dosing. (JX-1-0022 at 20:39-49.)

DFF70. The basis for Example 8 is a study run by Dr. Fein's company, CNF Pharma. The CNF in CNF Pharma stands for Cheng, Nardi, and Fein. The clinical study protocol for the CNF study is essentially a copy of the protocol for a Ferring clinical study called CS009. Dr. Fein did not design Ferring's CS009 protocol, but did have access to the protocol before being fired from Ferring. [Anticipated testimony of Dr. Fein, Mr. Vis.]

DFF71. Example 8 also includes a summary of the results of the study and includes the urine osmolality and urine output results for each subject in Tables 1-6 and Figures 1-9 of the common specification. (*See generally* JX-1-0023 to JX-1-0026 at 22:19-27:3; JX-1-0004 to JX-1-0012 at Figures 1-9.)

DFF72. Example 8 is the only example in the common specification that provides pharmacodynamic information (i.e., the duration of action for antidiuresis). (*See generally,* JX-1.) [Anticipated testimony of Dr. Spaans, Mr. Vis.]

DFF73. The common specification states that the results of Example 8 "confirm the low-dose hypothesis . . . and provide an empirical basis for further clinical studies in patients to evaluate low doses of desmopressin for such conditions as primary nocturnal enuresis, adult nocturia, incontinence, and central diabetes insipidus." (JX-1-0026 at 27:4-8.) In addition, the common specification states that Example 8 "demonstrates that desmopressin can produce this essential antidiuretic effect at much lower doses and lower blood concentrations than previously thought." (JX-1-0026 at 27:48-51.) The common specification theorizes that "[t]his may be adequate to produce the desired therapeutic effects for existing and potential new clinical indications for desmopressin." (JX-1-0025 to JX-1-0026 at 26:67-27:3.)

DFF74. None of the plasma concentrations recited in the Examples in the common specification fall within the plasma concentration ranges claimed in the patents in suit. Examples 1-7 and Comparative Examples 1-4 do not include any pharmacodynamic data, and Example 8 does not include any pharmacokinetic data, much less plasma concentration data. Further, the common specification does not correlate the plasma concentrations claimed in the asserted claims with the desired antidiuretic effect. [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

DFF75. The common specification includes specific examples of only three desmopressin formulations: an orodispersible formulation, an oral tablet formulation, and an i.v. formulation. [Anticipated testimony of Dr. Spaans, Mr. Vis, Dr. Mayersohn.]

F. Person of ordinary skill in the art

DFF76. A person of ordinary skill in the art ("POSITA") for the asserted claims of the patents in suit would be a team of individuals. This team would include a physician with a medical degree, as well as experience in diagnosing, treating, and/or prescribing medication to

treat patients who are in need of voiding postponement. The team would also include an individual with an advanced degree (e.g., a Ph.D. or Masters or PharmD or equivalent) in one of the pharmaceutical sciences and three to five years of experience in clinical pharmacology or drug formulation. [Anticipated testimony of Dr. Spaans.]

G. NOCDURNA

DFF77. Counterclaimants allege that the asserted claims are infringed through the use of Ferring's NOCDURNA product. (Stipulated Fact ¶ 25.)

DFF78. Ferring received approval for NOCDURNA on June 21, 2018. NOCDURNA is an orodispersible formulation of desmopressin indicated for the treatment of nocturia due to nocturnal polyuria in adults who wake up at least two times per night to urinate. (JX-5-0002.) [Anticipated testimony of Mr. Carter.]

DFF79. Ferring launched NOCDURNA in the United States on November 9, 2018. [Anticipated testimony of Mr. Carter.]

DFF80. NOCDURNA has gender specific dosing: 27.7 mcg of desmopressin acetate (equivalent to 25 mcg of desmopressin) daily for women and 55.3 mcg of desmopressin acetate (equivalent to 50 mcg of desmopressin) daily for men. (JX-5-0002.) The abbreviation "mcg" refers to micrograms, which is also abbreviated as "µg."

H. Pharmacology

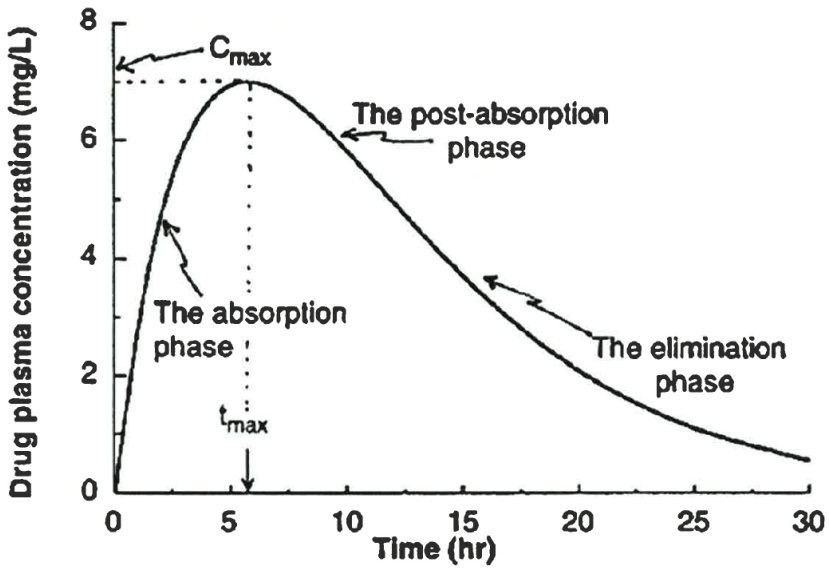
DFF81. At a broad level, pharmacology is the study of chemical substances, such as drugs, that interact with the human body through chemical and biological processes. [Anticipated testimony of Dr. Spaans.]

1. Pharmacokinetics

DFF82. Pharmacokinetics is one branch of pharmacology, which seeks to analyze the actions of the human body on a pharmaceutical drug compound. (Stipulated Fact ¶ 4.)

DFF83. Pharmacokinetics includes, for instance, measuring the time course of absorption of the drug into the bloodstream and the eventual clearance of the drug from the body. (Stipulated Fact ¶ 5.)

DFF84. In pharmaceutical drug development, researchers analyze many different pharmacokinetic parameters, which include the blood plasma concentration of the pharmaceutical drug absorbed into the bloodstream at different time intervals. This information can then be graphed as a function of time, as shown below:



[Anticipated testimony of Dr. Spaans.]

DFF85. As shown above, after a drug is administered to a subject, it is gradually absorbed into the bloodstream and the plasma concentration increases, reaches a maximum, and then returns towards the baseline. [Anticipated testimony of Dr. Spaans.]

DFF86. The maximum plasma concentration achieved after administration of a drug to a subject is known as the C_{max}. (Stipulated Fact ¶ 6.) The time it takes to reach the C_{max} is known as the T_{max}. (Stipulated Fact ¶ 7.)

DFF87. Total absorption is shown by the AUC, which is the total "area under the curve" of the plasma concentration graph. [Anticipated testimony of Dr. Spaans.]

DFF88. The plasma concentration of a single dose of a pharmaceutical drug reaches the C_{max}, when the rate of elimination equals and then exceeds the rate of absorption, and accordingly, the plasma concentration begins to diminish. [Anticipated testimony of Dr. Spaans.]

DFF89. The clearance rate of a pharmaceutical drug is reflected in the half-life of the drug ($T_{1/2}$), which is the time required for the blood concentration of drug in the body to decrease by 50%. [Anticipated testimony of Dr. Spaans.]

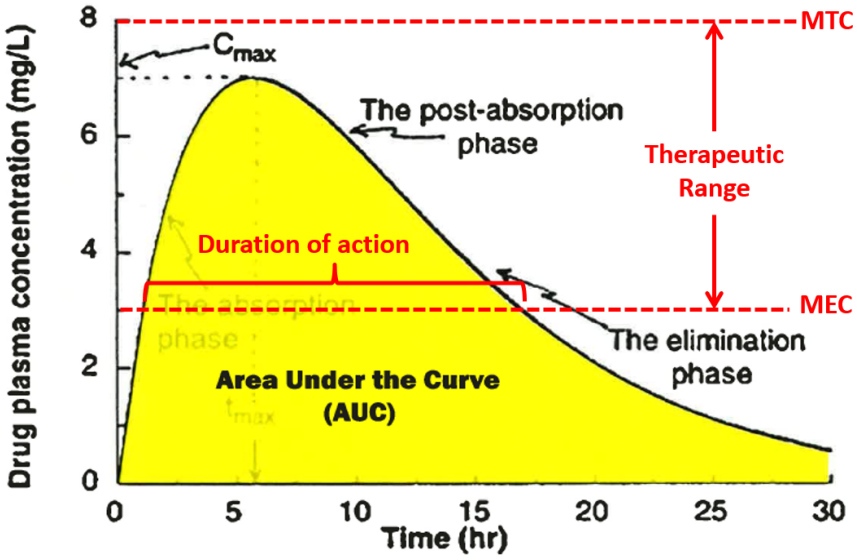
DFF90. Bioavailability is defined as the fraction of the administered dose of a drug that absorbs into the bloodstream. Bioavailability, like other pharmacokinetic parameters, may depend on the formulation, dosage form, and the route of administration. (Stipulated Fact ¶ 8.) [Anticipated testimony of Dr. Spaans.]

DFF91. Intravenous ("i.v.") administration of a drug is typically assumed to have 100% bioavailability because the drug is administered directly into the bloodstream. Other routes of administration, which rely on absorption into the bloodstream rather than direct injection, will have lower bioavailability. [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

2. Pharmacodynamics

DFF92. Pharmacodynamics is another branch of pharmacology, which seeks to analyze the pharmacological effect of a pharmaceutical drug on the body. (Stipulated Fact ¶ 9.)

DFF93. With respect to the graph below, the pharmacodynamic parameters are represented by the "duration of action," the "MEC," and the "MTC."



[Anticipated testimony of Dr. Spaans.]

DFF94. The "MEC" above represents the "minimum effective concentration," which is the minimum blood plasma concentration required to see a pharmacodynamic effect. The "MTC" above represents the minimum toxic concentration, which is the minimum blood plasma concentration where toxic side effects are seen. The therapeutic range for a drug is between the MEC and MTC, and the time that the blood plasma concentration remains within the therapeutic window (and thus is producing an effect) is known as the duration of action. [Anticipated testimony of Dr. Spaans.]

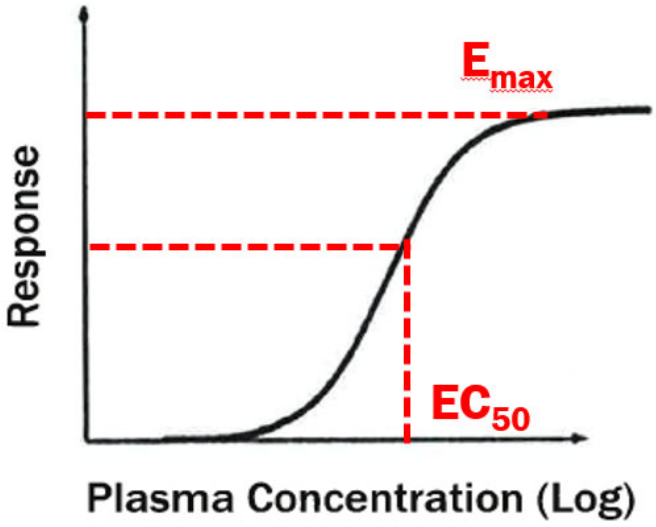
3. The relationship between pharmacokinetics and pharmacodynamics

DFF95. Pharmacokinetic and pharmacodynamic events overlap, and the concentration of drug in the blood (or plasma) and the rate at which that concentration changes over time are driving forces for pharmacodynamic events following drug dosing. (Stipulated Fact ¶ 10.)

DFF96. While the absolute dose administered affects the plasma concentrations, it is the plasma concentrations that determine the pharmacological response to the drug. (Stipulated Fact ¶ 11.)

DFF97. With an understanding of the pharmacokinetics and pharmacodynamics of a particular formulation, drug developers can develop a dose response relationship and use this relationship to select doses and potential formulations, and target plasma concentrations to produce the desired antidiuretic effect to treat patients. Generally, in order for the dose response relationship to be useful in predicting how different formulations or routes of administration for a particular drug will behave, the underlying pharmacokinetic and pharmacodynamic data must be robust and accurate. [Anticipated testimony of Dr. Spaans.]

DFF98. An example of a dose response curve is shown below:



As can be seen above, the dose-response curve begins at zero plasma concentration and zero pharmacodynamic effect. As the plasma concentration of the drug increases, the pharmacodynamic effect also increases. [Anticipated testimony of Dr. Spaans.]

DFF99. Typically, the relationship between the plasma concentration and pharmacodynamic effect is non-linear. In other words, small changes to plasma concentrations at the lower end of the spectrum produce larger changes in pharmacodynamic effect, but small changes to higher plasma concentrations result in smaller changes in pharmacodynamic effect. This is because, at higher plasma concentrations, the drug is reaching its maximum effect (shown as E_{max} in the graph above) and the curve reaches this maximum effect asymptotically. [Anticipated testimony of Dr. Spaans.]

DFF100. The point labeled EC_{50} in the above graph refers to the plasma concentration that produces 50% of the maximum pharmacodynamic effect, a parameter that is useful in describing the potency of a particular drug. [Anticipated testimony of Dr. Spaans.]

DFF101. Based on a knowledge of both the pharmacokinetics and the pharmacodynamics of the concentration-response curve, gained by an iterative process of clinical trials that connects dose to concentration to effect, drug developers may design doses to achieve target plasma concentrations and determine the doses and plasma concentrations that optimize the desired effect. For certain drugs, variability in bioavailability (effecting how much of the drug is absorbed) and/or pharmacodynamic response (affecting different individuals' sensitivities to the same plasma concentrations of a drug) can complicate such efforts considerably. Once this type of dose-ranging is complete, however, one can select the doses that best fit a therapeutic range of providing pharmacodynamic effect and avoiding adverse side effects. [Anticipated testimony of Dr. Spaans.]

4. Variability in pharmacokinetic and pharmacodynamic parameters

DFF102. One issue that arises in evaluating pharmacokinetic and pharmacodynamic parameters for drug development is the variability in the observed data. Typically,

pharmacologists use two primary measures of variability—standard deviation and the coefficient of variation ("CV"). [Anticipated testimony of Dr. Spaans.]

DFF103. The standard deviation is an expression of how far away the values in a particular data set are from the mean. Typically, approximately 68% of the values in a particular data set will fall within one standard deviation of the mean value. [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

DFF104. The CV, also known as the relative standard deviation, is another measure of variability in a data set. The CV is the ratio of the standard deviation to the mean and is generally expressed as a percentage. The CV provides an indication of precision and repeatability. Typically, pharmacokineticists rely on the CV to provide variability information regarding pharmacokinetic data.

DFF105. A data set that repeatedly gives the same (or nearly the same) values would have a low standard deviation and low CV, and the individual values would be close to the mean. For example, if the data set were 49 and 51, the mean would be 50, the standard deviation would be 1, and the CV would be 2%. In contrast, if the individual numbers vary widely, the standard deviation and CV will be higher, and the values may not be close to the mean. For example, if the data set were 0 and 100, the mean would be 50, the standard deviation would be 50, and the CV would be 100%. In the examples above, although the mean value is the same, it is only reasonably representative of the actual values in the first example, which is why, all things being equal, lower variability is preferable in drug development. [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

DFF106. In drug development, a POSITA would consider data to exhibit high intra-subject variability if the CV is above 30% for a reasonable number of study subjects. Similarly,

in drug development, a POSITA would consider data to exhibit high inter-subject variability if the CV is above 30%. [Anticipated testimony of Dr. Spaans.]

I. The pharmacokinetics and pharmacodynamics of desmopressin

DFF107. Although desmopressin is administered as desmopressin acetate (molecular weight 1183 g/mol), in the body, desmopressin converts from this salt form to the free base. Desmopressin is a relatively large molecule, with a molecular weight of approximately 1069 g/mol, when measured as a free base. [Anticipated testimony of Dr. Spaans.]

DFF108. Desmopressin formulations typically exhibit high variability. For example, the NOCTIVA label states that "[t]he mean (± S.D.) peak plasma concentration (Cmax) was 4.00 (± 3.85) pg/mL for the 0.83 mcg dose and 9.11 (± 6.90) pg/mL for the 1.66 mcg dose." (JX-6-0008.) This corresponds to a CV of 96.2% for the 0.83 µg dose and a CV of 75.7% for the 1.88 µg dose. [Anticipated testimony of Dr. Mayersohn, Dr. Murray.]

DFF109. Ferring's orodispersible tablet also exhibits high variability. For example, a Ferring clinical study designated CS021—a study on which Counterclaimants rely as support their infringement allegations—evaluated certain pharmacokinetic parameters for 60 µg, 120 µg, and 240 µg orodispersible formulations of desmopressin. (PX-22 at FERALL0000037.)

DFF110. In that study, the mean C_{max} was 4.033 pg/ml, 9.577 pg/ml, and 19.044 pg/ml for the 60 µg, 120 µg, and 240 µg doses, respectively. (*See* JX-12-0065 at Table 0-2.) The standard deviations for the mean C_{max} in CS021 were 1.548 pg/ml, 7.123 pg/ml, and 15.003 pg/ml. (JX-12-0065 at Table 9-2.) This results in a CV for the C_{max} numbers of 34.1%, 62.4% and 83.6% for the 60 µg, 120 µg, and 240 µg, respectively. (JX-12-0065 at Table 9-2.)

DFF111. The pharmacodynamic response (i.e., antidiuresis) for desmopressin exhibits similar variability. [Anticipated testimony of Dr. Juul.]

DFF112. Because of this variability in the pharmacokinetics and pharmacodynamics of desmopressin, it is not possible to accurately predict the desmopressin plasma concentrations or durations of action for an individual subject. In other words, the same formulation with the same dose, given to different individuals (or even the same individual at different times), will produce different desmopressin plasma concentrations and durations of action. In one individual, administration may produce almost no desmopressin plasma concentration (and thus no duration of action), while in another individual, it may produce many times the mean C_{max} with a correspondingly longer duration of action. [Anticipated testimony of Dr. Juul.]

II. The Asserted Claims Are Invalid under 35 U.S.C. § 112, ¶ 1

A. The asserted claims are invalid for lack of written description and for lack of enablement under the standards set forth by Judge Bryson in *Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F. Supp. 3d 566 (D. Del. 2018)

DFF113. The asserted claims of the patents in suit are all generic in nature, in that they are directed to methods of treating voiding disorders by administering to a patient an open-ended set of desmopressin formulations and doses that satisfy either the pharmacokinetic limitations (the asserted claims of the ’203 patent and asserted claims 6 and 7 of the ’321 patent) or the pharmacodynamic limitations (the asserted claims of the ’321 patent). (JX-1-0026 at cl. 6, 10, 11, 12, 13; JX-2-0027 to JX-2-0028 at cl. 3, 5, 6, 7, 12.) [Anticipated testimony of Dr. Spaans, Dr. Verbalis.]

DFF114. The pharmacokinetic limitations (i.e., the plasma concentrations) are functional limitations in that they describe the results that flow from a particular formulation, route of administration, and dose. [Anticipated testimony of Dr. Mayersohn.]

DFF115. Similarly, the pharmacodynamic limitations of the asserted claims of the ’321 patent (i.e., the antidiuretic durations of action) are functional limitations in that they describe the results that flow from a particular formulation, route of administration, and dose. [Anticipated testimony of Dr. Mayersohn.]

DFF116. The common specification includes no examples that meet any of the functional limitations of the claims. The disclosures in the table in column 17 of allegedly effective daily dose ranges for various routes of administration have no examples to teach or show that they are, in fact, effective to meet the functional limitations of the asserted claims or to provide therapeutic efficacy, nor would a POSITA expect all formulations for each route of

administration that have desmopressin doses in the disclosed ranges to meet the functional limitations of the asserted claims. [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

DFF117. Subject to the restrictions on the routes of administration in certain of the asserted claims, the asserted claims can encompass any desmopressin formulation and dose amount that meets the functional limitations of the claim. [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

DFF118. The common specification provides no guidance on any structural features of any given formulation or route of administration that would assist a POSITA in identifying the species that fall within the asserted generic claims. [Anticipated testimony of Dr. Mayersohn.]

DFF119. Because there is no single working example in the common specification that provides both the pharmacokinetic and pharmacodynamic data for a particular formulation, the predictive value of the data in the common specification is severely limited. In order for the data in the common specification to potentially have predictive value and allow extrapolation to other formulations and routes of administration, the common specification would need to disclose individual plasma concentration and individual pharmacodynamic response data. The individual pharmacokinetic data may allow one to create a model of the plasma concentration over time curves and use that model to predict the plasma concentrations over time for other formulations. Similarly, the individual pharmacokinetic and pharmacodynamic data allow for modeling of each individual concentration effect curve and allow the information to be aggregated to help build a predictive model, which potentially could then be used to provide an individual estimate of the duration of action when using a different formulation (e.g., a different dosage form or administration route) or a different study population (e.g., patients rather than healthy volunteers). [Anticipated testimony of Mr. Vis.]

DFF120. The data in the common specification is insufficient to allow a POSITA to model the plasma concentration over time curves (i.e., the pharmacokinetic effect) or the antidiuretic effect (i.e., the pharmacodynamic effect) as a function of desmopressin blood plasma concentration. Without these data, which are missing from the common specification, it is not possible to extrapolate how another dosage form would work or to extrapolate how any specific individual (much less a patient rather than a healthy volunteer) in another population would react. [Anticipated testimony of Dr. Spaans, Mr. Vis.]

DFF121. While asserted claim 6 of the '203 patent and asserted claim 12 of the '321 patent limit their respective independent claims to transmucosal routes of administration, (JX-1-0026 at cl. 6; JX-2-0028 at cl. 12), each of the other asserted claims include transmucosal routes of administration in addition to other routes of administration. [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

DFF122. Transmucosal administration/delivery includes administering or delivering desmopressin to any mucosal tissue, including the mucosa in the mouth and gastrointestinal tract. Accordingly, the transmucosal route of administration includes, at least administration of, oral tablets, orodispersible tablets, wafers, films, effervescent formulations, eye drops, sublingual formulations, supralingual formulations, buccal formulations, suppositories, and enemas. (*See* JX-1-0021 at 17:1-15.) [Anticipated testimony of Dr. Mayersohn.]

DFF123. Each of these different types of formulations may be formulated with different types and quantities of excipients, which will affect the release and absorption characteristics of the desmopressin in the formulation, resulting in different plasma concentration curves and different durations of action. [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

DFF124. Accordingly, the asserted claims with transmucosal limitations still cover an open-ended set of desmopressin formulations that may be used to treat in accordance with the claimed methods. The ability to produce an effect within the claimed methods depends entirely on whether the particular formulation meets the claimed functional limitations. Indeed, the asserted claims even cover any later developed desmopressin formulations that meet the functional limitations. [Anticipated testimony of Dr. Mayersohn.]

DFF125. For example, looking at just the orodispersible tablet, assuming that each formulation will contain up to four constituent excipients besides desmopressin (the number of excipients in Examples 1 through 6), there are a total of twenty-four possible formulations. If each of the excipients in the above example can occur in one of five different amounts, there are approximately 2,880 different combinations, just for the orodispersible tablet alone. Assuming that transmucosal formulations only include oral tablets, orodispersible tablets, wafers, films, effervescent formulations, eye drops, sublingual formulations, supralingual formulations, buccal formulations, suppositories, and enemas and that each different type of formulation also has four excipients that can occur in five different amounts, there are approximately 31,680 different formulations that could potentially fall within the scope of the asserted claim 6 of the ’203 patent and asserted claim 12 of the ’321 patent, assuming that the functional limitations are met. [Anticipated testimony of Dr. Mayersohn.]

DFF126. The common specification is, at most, focused on teaching a sublingual dosage form, which is a formulation subset for the transmucosal route of administration. The asserted claims, other than asserted claim 6 of the ’203 patent and asserted claim 12 of the ’321 patent include routes of administration in addition to the transmucosal route of administration. The number of formulations that may be used to treat according to those claimed methods will be

even higher, and the common specification provides no teaching or disclosure of how these other routes of administration will result in low plasma concentrations, have therapeutic efficacy, or reduce the risk of hyponatremia. [Anticipated testimony of Dr. Mayersohn.]

DFF127. Formulation science is an unpredictable art that requires experimentation to determine if a particular formulation will be effective. The common specification does not provide any direction or teaching of even one formulation that meets both the pharmacokinetic and pharmacodynamic limitations of the asserted claims. The common specification does not disclose any working examples of formulations that meet the pharmacokinetic parameters of the asserted claims. The common specification does not disclose any working examples of claimed formulations that meet the pharmacodynamic limitations of the asserted claims. [Anticipated testimony of Dr. Spaans, Mr. Vis, Dr. Mayersohn.]

DFF128. In order to determine if a particular formulation within the potential myriad of formulations would meet the functional limitations of the asserted claims, a POSITA would need to conduct a clinical trial. Based on the results of the clinical trial, if the tested formulation did not meet the claim limitations, a POSITA may then need to modify the formulation and then conduct additional clinical trials to determine if the new formulation met the functional limitations of the asserted claims. [Anticipated testimony of Dr. Spaans.]

DFF129. Example 7 indicates that the "pharmacokinetics of desmopressin is linear, when administered as the orodispersible dosage form of Example 4, 5 or 6." (JX-1-0022 at 20:9-11.) First, as with any data set, a POSITA would know that the data will be much more accurate for interpolation, rather than extrapolation. In other words, based on the data provided, interpolating the pharmacokinetic parameters for doses of desmopressin between 200 µg and 800

µg will be reasonably accurate because those interpolations are based on actual data. [Anticipated testimony of Dr. Spaans.]

DFF130. In contrast, when using the data to extrapolate (i.e., to estimate what may happen at values outside of the upper and lower bounds of a particular data set), a POSITA would know that the extrapolated estimates are more uncertain. For example, attempting to extrapolate the data in Example 7 to doses higher than 800 µg or doses lower than 200 µg introduces error, which will likely be larger the further from the actual data one extrapolates. [Anticipated testimony of Dr. Spaans.]

DFF131. Further, a POSITA would know that Example 7's statement is limited to the specific dosage form tested—i.e., an orodispersible tablet with excipients in the same ratios as those in Examples 4, 5, and 6. This statement is not necessarily true for other dosage forms, even those dosage forms that have the same qualitative composition but a different quantitative composition (i.e., the same excipients, but different amounts). [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

DFF132. Similarly, the common specification states that the doses of desmopressin "may be administered by any method known in the art" and presumably by any formulation. (JX-1-0020 at 16:51-52 and JX-1-0021 at 17:24-29.) However, as explained above, the common specification does not disclose dosage forms, formulations, or routes of administration that produce plasma concentrations within the claimed range, nor does it teach how a specific formulation will achieve a specified plasma concentration or pharmacodynamic effect. [Anticipated testimony of Dr. Spaans.]

DFF133. In order to determine an appropriate dose for a particular dosage form with a particular formulation and a particular route of administration, it is necessary to know the

bioavailability of the specific dosage form, as formulated. The bioavailability can be affected by many variables, including the excipients used, the relative amounts of the excipients to each other and to the drug, and the method of manufacture. And the only way to determine the bioavailability of a particular dosage form with a particular formulation for a particular route of administration is to test the dosage form in a human clinical trial. Even relatively small changes in the formulation can affect the bioavailability. [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

DFF134. As such, for each new dosage form it would be necessary to conduct a clinical trial to determine the bioavailability and thus the resulting plasma concentrations. Even putting aside the sheer volume of tests that would be necessary to gain any understanding concerning the multitude of covered formulations and methods of administration, as noted above, such clinical trials would be neither trivial nor predictable. [Anticipated testimony of Dr. Spaans.]

B. The asserted claims of the ’203 patent and claims 6 and 7 of the ’321 patent are invalid for lack of written description because there is no support for the claimed plasma concentration ranges

DFF135. The asserted claims of the ’203 patent and claims 6 and 7 of the ’321 patent are invalid for lack of written description because there is no support for the claimed desmopressin plasma concentration ranges.

DFF136. Asserted claim 6 of the ’203 patent, which depends from unasserted claim 1, requires “maintaining the [desmopressin plasma] concentration within the range of about 0.5 pg/ml and 10 pg/ml for about four to six hours.” (JX-1-0026 at cl. 1, 6.)

DFF137. Asserted claims 10 and 11 of the '203 patent each require "establish[ing] a maximum serum/plasma desmopressin concentration no greater than 10 pg/ml." (JX-1-0026 at cl. 10, 11.)

DFF138. Asserted claim 12 of the '203 patent requires "a serum/plasma desmopressin concentration no greater than about 5 pg/ml." (JX-1-0026 at cl. 12.)

DFF139. Asserted claim 13 of the '203 patent requires "a maximum serum/plasma desmopressin concentration greater than 0.1 pg/ml and less than 10 pg/ml." (JX-1-0026 at cl. 13.)

DFF140. Claim 6 of the '321 patent requires "a plasma/serum desmopressin concentration in the patient of a maximum of no more than about 10 pg/ml." (JX-2-0027 at cl. 6.)

DFF141. Claim 7 of the '321 patent requires "a plasma/serum desmopressin concentration in the patient of a maximum of no more than about 5 pg/ml." (JX-2-0027 at cl. 7.)

DFF142. The common specification states that the doses of desmopressin "may be administered by any method known in the art" and presumably by any formulation. (JX-1-0020 at 16:51-52 and JX-1-0021 at 17:24-29.)

1. The ranges of plasma concentrations claimed are too broad

DFF143. A range from 0.5 pg/ml to 10 pg/ml represents a twenty-fold increase in the plasma concentration, which is an enormous range. A range from 0.1 pg/ml to 10 pg/ml represents a one hundred-fold variation in the plasma concentration, which is five times greater than the already large increase from 0.5 pg/ml to 10 pg/ml. Moreover, asserted claims 10, 11, and 12 of the '203 patent and asserted claims 6 and 7 of the '321 patent claim only an upper limit, not a lower limit, such that any amount greater than zero is included in the range. [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

DFF144. The common specification only discusses the claimed plasma concentration ranges in column 16, stating that: "[i]n accordance with the present invention, plasma/plasma/serum desmopressin concentrations following administration of the pharmaceutical composition of the invention preferably range from about 0.1 pg/mL to about 10.0 pg/mL, and more preferably from about 0.5 pg/mL to about 5 pg/mL." (JX-1-0020 at 16:46-50.) [Anticipated testimony of Dr. Spaans.]

DFF145. The common specification does not disclose a range of 0.5 pg/ml to 10 pg/ml as claimed in asserted claim 6 of the '203 patent. (JX-1-0026 at cl. 1, 6.) [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

DFF146. The common specification does not disclose why plasma concentrations within the claimed ranges are effective to treat patients suffering from the claimed disease states or otherwise in need of voiding postponement, or if all plasma concentrations within the claimed ranges are effective to treat patients. [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

DFF147. A range as broad as those claimed in the asserted claims of the '203 patent and claims 6 and 7 of the '321 patent does not provide a specific (or at least a more specific) target plasma concentration range that will provide not only the desired plasma concentration range but also an antidiuretic effect, as required by the claims. Indeed, the data disclosed in the common specification indicate that not all plasma concentrations within the claimed range are effective. [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

2. The Examples do not teach formulations or methods of treatment that fall within the claimed ranges

DFF148. Only two examples in the common specification disclose pharmacokinetic data—Example 7 and Comparative Example 4. (*See generally*, JX-1.)

DFF149. Example 7 discloses mean pharmacokinetic parameters for the orodispersible tablets of Examples 4, 5, and 6 and states that the maximum desmopressin plasma concentrations (C_{max}) were 14.25 pg/ml, 30.21 pg/ml, and 65.25 pg/ml, respectively. (JX-1-0022 at 20:2-4.) None of these values are below the upper limits claimed in the asserted claims of the '203 patent or claims 6 and 7 of the '321 patent. [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

DFF150. Similarly, Comparative Example 4 reports the maximum desmopressin plasma concentrations after administration of the conventional oral tablets from Comparative Examples 2 and 3. (JX-1-0022 at 20:27-32.) The C_{max} for these formulations was 13.2 pg/ml and 15.0 pg/ml, respectively. (JX-1-0022 at 20:30-32.) Neither of these values are within the limits claimed in the asserted claims of the '203 patent or claims 6 and 7 of the '321 patent. [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

DFF151. Example 8 reports the results of a clinical trial where three different doses of desmopressin were administered by steady intravenous infusion over two hours. (JX-1-0022 at 20:39-49.) [Anticipated testimony of Mr. Vis.]

DFF152. With respect to pharmacokinetic parameters, Example 8 states that:

> Pharmacokinetic parameters were derived from the individual concentration versus time curves of desmopressin, i.e., AUC (area under the plasma concentration time curve to infinity), C_{max} (maximum plasma concentration observed), t_{max} (time of C_{max} after dosing), CL (total systemic clearance), V_z (volume of distribution during the terminal phase), AUC_t (area under the plasma concentration time curve from time zero to time t), λz (first order rate constant associated with the terminal (log-linear) portion of the plasma concentration time curve estimated via linear regression of the time vs. log of concentration) and $t_{1/2}$ (terminal half life).

(JX-1-0023 at 22:6-17.) Example 8 does not, however, report any C_{max}, AUC, T_{max}, CL, V_z, AUC_t, or $T_{1/2}$ parameters. (JX-1-0022 to JX-1-0026 at Example 8.) [Anticipated testimony of Mr. Vis.]

DFF153. The plasma concentrations were allegedly calculated for Example 8, but Example 8 does not disclose the method of calculation or the calculated plasma concentration values. (JX-1-0022 to JX-1-0026 at Example 8.) [Anticipated testimony of Mr. Vis.]

DFF154. Without knowing the method of calculation or the actual calculated numbers, one cannot verify the data or confirm whether the plasma concentrations were within the claimed ranges. [Anticipated testimony of Mr. Vis.]

DFF155. Further, all three of the clinical examples describe results in healthy subjects, not patients, and the asserted claims of the '203 patent and claims 6 and 7 of the '321 patent are each directed to treatment of a "patient" or inducing an antidiuretic effect in a "patient." A POSITA would know that pharmacokinetic results from healthy subjects cannot be assumed to correlate to such results in actual patients. [Anticipated testimony of Dr. Spaans, Dr. Mayersohn, Mr. Vis.]

DFF156. In order for the data in the common specification to potentially have predictive value to allow extrapolation of the plasma concentrations to other formulations and routes of administration, the common specification would need to disclose individual plasma concentrations and individual pharmacodynamic response data. These individual data might allow for modeling of each individual concentration curve and allow the information to be aggregated to help build a predictive model, which potentially could then be used to provide an individual estimate of the plasma concentrations when using a different formulation (e.g., a different dosage form or administration route) or a different study population (e.g., patients rather than healthy volunteers). [Anticipated testimony of Mr. Vis.]

DFF157. However, the data in the common specification are insufficient to allow a POSITA to model the desmopressin blood plasma concentration curve as a function of time, and

thus it is not possible to extrapolate how another dosage form would work or to extrapolate how any specific individual (much less a patient rather than a healthy volunteer) in another population would react. [Anticipated testimony of Mr. Vis.]

C. The asserted claims of the '321 patent and claim 6 of the '203 patent are invalid for lack of written description and for lack of enablement because there is no support for the claimed durations of action

DFF158. Asserted claims 3, 5, 6, 7, and 12 of the '321 patent and asserted claim 6 of the '203 patent are invalid for lack of written description and lack of enablement because there is no written description support or enabling disclosure for the claimed durations of action.

DFF159. Claims 3, 5, 6, and 7 of the '321 patent are dependent claims and each depends from unasserted independent claim 1. (JX-2-0027 at cl. 3, 5, 6, and 7.)

DFF160. Unasserted claim 1 of the '321 patent requires that the amount of desmopressin in the bloodstream be "therapeutically effective to produce an antidiuretic effect lasting for no more than between about 4 and about 6 hours." (JX-2-0027 at cl. 1.)

DFF161. Unasserted claim 8 of the '321 patent requires that the amount of desmopressin administered be "sufficient to produce in the patient a urine osmolality ranging above about 300 mOsm/kg for less than about 5 hours after administration." (JX-2-0027 at cl. 8.)

DFF162. Claim 12 of the '321 patent is a dependent claim that depends from either claim 1 or claim 8. (JX-2-0028 at cl. 12.) To the extent claim 12 depends from claim 1, it also requires that the amount of desmopressin in the bloodstream be "therapeutically effective to produce an antidiuretic effect lasting for no more than between about 4 and about 6 hours." (JX-2-0027 at cl. 1.) To the extent that claim 12 depends from claim 8, it also requires that the amount of desmopressin administered be "sufficient to produce in the patient a urine osmolality

ranging above about 300 mOsm/kg for less than about 5 hours after administration." (JX-2-0027 at cl. 8.)

DFF163. Claim 6 of the '203 patent is a dependent claim and depends from unasserted independent claim 1 of the '203 patent. (JX-1-0026 at cl. 6.)

DFF164. Unasserted claim 1 of the '203 patent requires maintaining a plasma concentration of desmopressin "within the range of about 0.5 pg/ml and 10 pg/ml for about four to six hours."

DFF165. The claim limitation "lasting for no more than between about 4 and about 6 hours" in claim 1 requires that the antidiuretic effect last for a time period close to about 4 hours to about 6 hours. (JX-2-0027 at cl. 1.) [Anticipated testimony of Mr. Vis, Dr. Mayersohn.]

DFF166. The claim limitation "for less than about 5 hours after administration" in claim 8 requires that the antidiuretic effect last for a time period close to about five hours, counting from the time desmopressin is administered, where the indication of antidiuretic effect is a urine osmolality above 300 mOsmol/kg. (JX-2-0027 at cl. 8.) [Anticipated testimony of Mr. Vis, Dr. Mayersohn.]

DFF167. The claim limitation "for less than about 5 hours after administration" requires that the urine osmolality must start below the 300 mOsm/kg threshold, increase to above 300 mOsm/kg, and decrease to less than 300 mOsm/kg. (JX-2-0027 at cl. 8.) [Anticipated testimony of Dr. Mayersohn.]

DFF168. The claim limitation "within the range of about 0.5 pg/ml and 10 pg/ml for about four to six hours" is to achieve a duration of action of approximately four to six hours. [Anticipated testimony of Dr. Mayersohn.]

1. Example 8 sets forth an explicit methodology for calculating duration of action as a function of urine osmolality over time

DFF169. The urine osmolality data for each of the eight subjects from Example 8 are set forth in Tables 1 through 3 in the common specification. Each of the tables includes urine osmolality from twenty minutes before (-20 minutes) the infusion began through six hours (360 minutes) after the infusion began. (JX-1-0023 to JX-1-0024 at Table 1, 2, 3.) Table 1 contains the data for the 0.5 ng/kg infusion; Table 2 contains the data for the 1.0 ng/kg infusion; and Table 3 contains the data for the 2.0 ng/kg infusion. (JX-1-0023 to JX-1-0024 at Table 1, 2, 3.) [Anticipated testimony of Mr. Vis.]

DFF170. As can be seen in the tables, at certain times, there is no urine osmolality data, which indicates either (i) that the subject did not void or (ii) that the subject was no longer participating in the study (as a result of having been censored out based on three consecutive urine volumes greater than 10 ml/min). [Anticipated testimony of Mr. Vis.]

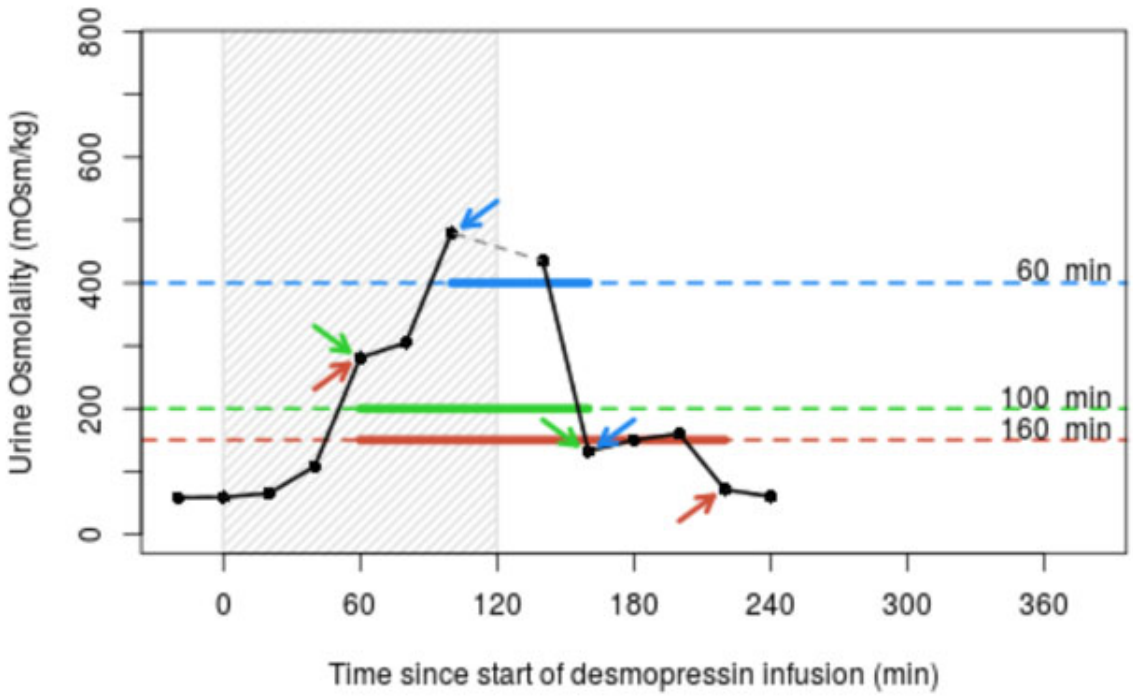
DFF171. The text of Example 8 is clear that the duration of action is based on urine osmolality and gives three specific thresholds to determine duration of action: 150, 200, and 400 mOsm/kg. (JX-1-0023 at 21:26-34.) Example 8 defines "duration of action" as the "time from 'onset' to 'end' action" and explains how to calculate the duration of action, stating that it is "the time from onset of action (i.e., the first time after dose administration where urine osmolality was [more] than 150 mOsm/kg) to end of action (the first subsequent time where urine osmolality was less than 150 mOsm/kg and confirmed at the next interval unless the first subsequent time was the last observation point)." (JX-1-0023 at 21:26-32.) Example 8 states that "[t]he second and third estimation used 200 mOsm/kg and 400 mOsm/kg as cut off levels for 'onset' and 'end' of action, respectively." (JX-1-0023 at 21:32-34.) [Anticipated testimony of Mr. Vis.]

DFF172. Example 8 defines the onset of action as the first time after dose administration where the urine osmolality exceeds the threshold limit (either 150, 200, or 400 mOsm/kg). (JX-1-0023 at 21:26-29.) Example 8 defines the offset of action as the first subsequent time where urine osmolality was less than the threshold and then confirmed at the next interval unless the first subsequent time was the last observation point. (JX-1-0023 at 21:29-32.) [Anticipated testimony of Mr. Vis.]

DFF173. Example 8 also explains that "[s]ubjects with no 'end' of action, with respect to the definition were censored at the time their urinary output returns to baseline (exceeds 10 mL/min) and/or the time where the over-hydration procedure stopped." (JX-1-0023 at 21:34-38.) In other words, individuals who had no offset of action were censored (i.e., were considered to have an offset of action) at either (i) the time the individual's urinary output exceeds 20 ml/min, or (ii) the time where the overhydration procedure was stopped (six hours). [Anticipated testimony of Mr. Vis.]

DFF174. According to Example 8, the duration of action is defined as the difference between the onset and offset of action. (JX-1-0023 at 21:22-26.) [Anticipated testimony of Mr. Vis.]

DFF175. For the data shown below, the three thresholds are shown in red (150 mOsm/kg), green (200 mOsm/kg), and blue (400 mOsm/kg); the first in time arrow indicates the onset of action, and the last in time arrow indicates the offset of action. The bold line represents the duration of action with the numerical duration shown on the right hand side of the graph. For this example, the duration of action is 160 minutes if the threshold is 150 mOsm/kg, 100 minutes if the threshold is 200 mOsm/kg, and 60 min if the threshold is 400 mOsm/kg. [Anticipated testimony of Mr. Vis.]



2. When calculated according to the methodology from Example 8, the durations of action based on urine osmolality do not support a duration of action of "between about four to about six hours" as required by the asserted claims

DFF176. According to Example 8, "[a]ll three doses (I.V. infusions) of desmopressin produced a measureable, antidiuretic effects in terms of increased urine concentration (osmolality) . . . ." (JX-1-0023 at 22:19-21.) Column 22 of the common specification indicates that the durations of antidiuretic effect "was approximately 180 minutes for the 0.5 ng/kg dose, 240 to 280 minutes for the 1.0 ng/kg dose and 360 minutes for the 2.0 ng/kg dose." (JX-1-0023 at 22:36-38.) The common specification then states that "[t]he pharmacodynamic duration of action was also proportional to the dose with the 1.0 and 2.0 ng/kg doses providing durations of 4 to 6 hours." (JX-1-0025 at 26:65-67.)

DFF177. These conclusions regarding Example 8 are not based on the methodology and data presented in Example 8. Analyzing the duration of action based on the protocol set forth

in Example 8 makes clear that the durations of action are overstated and were not calculated according to the procedure in Example 8. [Anticipated testimony of Mr. Vis.]

DFF178. If the durations of action are calculated according to the methodology set forth in Example 8, the durations of action are significantly shorter than the alleged "duration of antidiuretic effect." The appropriately calculated durations of action are shown below:

Subject	0.5 ng/kg			1.0 ng/kg			2.0 ng/kg		
	150	200	400	150	200	400	150	200	400
1	0	0	0	160	100	60	280	280	220
2	0	0	0	140	100	20	260	240	140
3	140	100	20	240	200	140	***320***	300	240
4	0	0	0	60	20	0	180	160	80
5	0	0	0	100	80	0	280	220	120
6	300	260	140	***320***	***320***	***320***	***320***	***320***	***320***
7	0	0	0	120	100	0	300	300	280
8	0	0	0	140	120	0	***320***	***320***	260
Mean	55	45	20	160	130	68	283	268	208
SD	110	94	49	83	91	113	47	57	85
CV%	201	208	245	52	70	168	17	21	41
Median	0	0	0	140	100	10	290	290	230
Min	0	0	0	60	20	0	180	160	80
Max	300	260	140	320	320	320	320	320	320

[Anticipated testimony of Mr. Vis.]

DFF179. The data in Example 8 do not support a duration of action of "between about four and about six hours" as required by claims 3, 5, 6, 7, and 12. For example, looking at the 0.5 ng/kg dose, only two of the eight individuals showed a duration of action at all, regardless of which threshold value was used. Further the means of the individual durations of action for the 0.5 ng/kg dose are 55 minutes, 45 minutes, and 20 minutes. These values are 31%, 25%, and 11% of the duration of action claimed in the common specification for the 0.5 ng/kg dose. Similarly, the durations of action for the 1.0 ng/kg and 2.0 ng/kg doses are also overstated in the common specification. [Anticipated testimony of Mr. Vis, Dr. Mayersohn.]

DFF180. Other than Example 8, the common specification does not include any further analysis or information that would support the durations of action claimed in the asserted claims of the '321 patent. [Anticipated testimony of Dr. Mayersohn, Mr. Vis.]

DFF181. Further, to the extent that the duration is based on mean data for urine osmolality, it is incorrect and overstated. Due to the censoring of the data, the data is biased to show a longer duration of action than actually is present in the data. This is because, when the effect in a particular subject wears off, hyperhydration in that subject is ended and urine samples (which would provide information regarding urine output and urine osmolality) are no longer collected. Because of this censoring, the mean data for a specific time point includes only those subjects where urine was collected and who are still showing an effect. As the number of subjects decreases, the total number of individuals is reduced and only values for those individuals is recording, thus artificially increasing the apparent duration of action. [Anticipated testimony of Mr. Vis.].

3. There is no written description support or enabling disclosure for a duration of action of less than about five hours after administration

DFF182. Claim 8, from which claim 12 also depends, requires a duration of action of "less than about five hours after administration" where the duration is defined by urine osmolality exceeding 300 mOsm/kg. (JX-1-0026 at cl. 8.) However, the 300 mOsm/kg threshold is not disclosed in the common specification. (*See generally* JX-1.)

DFF183. The data in Example 8 make clear that the lower doses are insufficient to achieve a duration of action even approaching five hours. Further, even at higher doses, some individuals do not approach the required duration of action and some individuals exceed the duration of action. [Anticipated testimony of Dr. Mayersohn.]

4. Determining how to treat a patient to achieve the claimed durations of action would require undue experimentation

DFF184. As discussed above, formulation science is an unpredictable art that requires experimentation to determine if a particular formulation will be effective to achieve a specific pharmacodynamic effect (here, the durations of action claimed in the asserted claims of the '321 patent). Without the individual pharmacokinetic and pharmacodynamic data from the administration of a particular formulation in humans, one cannot develop the individual concentration-effect curves. Without these individual concentration-effect curves, one cannot build a predictive model to provide an individual estimate of the duration of action when using a different formulation (e.g., a different dosage form or administration route) or a different study population (e.g., patients rather than healthy volunteers). [Anticipated testimony of Mr. Vis.]

DFF185. If one attempted to calculate individual plasma concentration curves based on estimated data, it would still not allow for reliable extrapolation, because basing an extrapolation on estimated (rather than empirical) data will only compound the error and lead to unpredictable results. [Anticipated testimony of Mr. Vis.]

D. Asserted claim 12 of the '321 patent is invalid for lack of written description because there is no support for the "300 mOsm/kg" limitation

DFF186. Example 8 establishes three urine osmolality thresholds for determining the duration of action of antidiuretic effect—150 mOsm/kg, 200 mOsm/kg, and 400 mOsm/kg. (JX-1-0023 at 21:22-34.) These three urine osmolality thresholds are the only urine osmolality thresholds disclosed in the common specification. (*See* JX-1.)

DFF187. The 300 mOsm/kg threshold only appears in the text of claim 8 of the '321 patent. (*See* JX-1; JX-2-0027 at cl. 8.) There is no teaching or discussion of the 300 mOsm/kg urine osmolality threshold in the common specification. [Anticipated testimony of Dr. Spaans.]

E. The asserted claims are invalid for lack of written description and for lack of enablement because there is no support for the claimed methods

DFF188. Because the common specification fails to disclose a specific dose or dose range for all dosage forms and routes of administration covered by the asserted claims, the common specification does not provide a practicing physician with enough information to know which dosage forms and routes of administration would achieve the claimed therapeutic effects and other recited properties (e.g., plasma concentrations), and which would not. [Anticipated testimony of Dr. Verbalis]

DFF189. While the common specification broadly lists the things physicians deal with such as dose ranges and dosage forms (*see* ¶¶ DFF52-DFF60), the only specific combinations of doses, dosage forms, and routes of administration described in the common specification are found in the examples:

- Examples 1-7 describe **orodispersible dosage forms** (i.e., fast-dissolving tablets; "ODT") of **200, 400, and 800 µg**;
- Example 8 describes solutions administered by i.v. infusion over 2 hours of 0.5 ng/kg, 1.0 ng/kg, and 2.0 ng/kg in 100 mL wherein the doses were roughly 35 ng, 70 ng, and 140 ng doses over 2 hours.

(JX-1-0021 at 17:32 *et seq.*) Examples 1-7 do not disclose anything with respect to therapeutic effects—they do not describe administration of desmopressin that induces voiding postponement, induces an antidiuretic effect, or treats specific voiding disorders such as nocturia, PNE, or incontinence. [Anticipated testimony of Dr. Verbalis]

DFF190. The only example even arguably supportive of the claimed therapeutic effects of the claimed methods is Example 8, which reports the results for urine output and urine osmolality but is limited to solutions administered by i.v. infusion—a dosage form and route of administration that (i) is outside the scope of the asserted claims, (ii) would never be used in practice, and (iii) is not informative as to any other dosage form or route of administration with

respect to meeting the claimed therapeutic effects (or the other recited properties) of the asserted claims. In addition, the study in Example 8 was performed in healthy volunteers without any discussion or teaching of how the study results could correlate to methods of administering desmopressin to patients to treat voiding disorders, such as those recited in asserted claims 6, 11, 12, and 13 of the '203 patent and claim 5 of the '321 patent. [Anticipated testimony of Dr. Verbalis]

DFF191. The common specification also notes that the results of the study reported in Example 8—the only teaching in the patents in suit of any dosage form or route of administration inducing an antidiuretic effect (though without data showing voiding postponement or treatment of a voiding disorder)—"provide[s] an empirical basis for further clinical studies in patients to evaluate low doses of desmopressin for such conditions as [PNE], adult nocturia, incontinence and [CDI]." (JX-1-0026 at 27:4-8.) This language suggests that this study was only the first study and does not provide any disclosure on whether other dosage forms and routes of administration (*see* JX-1-0020 to JX-1-0021 at 16:46-17:23) would achieve the therapeutic effects—as well as the other properties (e.g., blood plasma concentrations)—recited in the asserted claims. In other words, the disclosure in Example 8 could not be used to determine how another dosage form or route of administration could be used to achieve the claimed therapeutic effects. Instead, Example 8 was just an invitation to further experiment; it provides only a limited description of the general concept that low doses of desmopressin for treating voiding disorders should be evaluated. [Anticipated testimony of Dr. Verbalis]

DFF192. In view of the above, the common specification does not adequately teach that patients in need of antidiuresis or voiding postponement, or that have voiding disorders

(which require different dosing and durations of action[3] depending on the disorder and the patient), could be treated by the seemingly limitless combinations of dose ranges, dosage forms, and routes of administration described in the common specification (JX-1-0020 to JX-1-0021 at 16:46-17:23). For any given:

> (i) voiding disorder (i.e., a *patient* (a) suffering from nocturia, PNE, or incontinence, (b) in need of an antidiuretic effect, or (c) in need of voiding postponement),
>
> (ii) dosage form, and
>
> (iii) route of administration,

a physician would expect to be provided with a dosage form and some explanation that each individual disorder (i.e., a *patient* (a) suffering from nocturia, PNE, or incontinence, (b) in need of an antidiuretic effect, or (c) in need of voiding postponement) had been or could be treated effectively with certain doses (or dose ranges) of that dosage form. The common specification fails to provide that necessary information. [Anticipated testimony of Dr. Verbalis]

DFF193. In view of the above, the common specification fails to demonstrate that Dr. Fein was in possession of the methods for achieving the recited therapeutic effects for all of the dosage forms and routes of administration covered by the claims. The disclosure simply does not allow persons of ordinary skill in the art to recognize that Dr. Fein invented the claimed methods. [Anticipated testimony of Dr. Verbalis]

DFF194. Also in view of the above, the specification does not teach a practicing physician how to use the claimed methods. The specification does not provide sufficient information for a person of ordinary skill in the art to be able to tell which doses, dosage forms, and routes of administration can be used to achieve the claimed methods and which cannot. The

[3] The preferred durations are 4-24 hours for CDI, 8-10 hours for PNE, and 4-6 hours for nocturia.

claimed methods are quite complicated and, despite the decades-old history of desmopressin treatments for certain voiding disorders, the predictability of the art is limited even for individual patients. Furthermore, a significantly larger volume of experimentation than what is provided in the patents in suit would be required to use the claimed methods with the seemingly limitless combinations of dosage forms, routes of administration, and doses provided in the common specification, that theoretically achieve the claimed therapeutic effects. Therefore, the disclosure does not enable one of ordinary skill in the art to use the claimed methods. [Anticipated testimony of Dr. Verbalis]

F. The asserted claims of the '321 patent are invalid for lack of written description because there is no support for the claimed reduction of the risk of hyponatremia

1. Hyponatremia and Dr. Fein's claimed method of reducing its risk

DFF195. The common specification refers to hyponatremia generally and acknowledges that it is a concern when treating patients with desmopressin, but it does not refer to sodium serum levels, whether those that define the condition or those allegedly measured in Example 8. (*See* JX-1-0013 at 2:15-19; JX-1-0020 at 16:29-42; JX-1-0026 at 27:4-8; 27:18-24.). [Anticipated testimony of Dr. Verbalis]

DFF196. It is common knowledge in the medical field, particularly as it relates to treatment of various voiding disorders—inducing voiding postponement and inducing an antidiuretic effect in patients—that the use of desmopressin is associated with a risk of hyponatremia as a result of desmopressin-induced water retention. (*See, e.g.,* DX-1-0002.) [Anticipated testimony of Dr. Verbalis]

DFF197. The FDA requires most desmopressin treatments (including NOCTIVA, which was developed by Dr. Fein and Counterclaimants) to be accompanied by serum sodium

level monitoring programs and fluid moderation. (*See* JX-6-0001; JX-5-0001.) [Anticipated testimony of Dr. Verbalis]

DFF198. The common specification suggests that "reducing the risk that the patient develops hyponatremia" (*see* JX-2-0027 to JX-2-0028 at cl. 3, 5-7, and 12 (when dependent on claim 1)) can be accomplished by lowering the dose of desmopressin (*see* JX-1-0013 at 2:15-20 (stating that doses lower than those that cause hyponatremia are preferable "if the same desired effect could be produced")), which in turn shortens the duration of action of desmopressin. [Anticipated testimony of Dr. Verbalis]

2. There are many factors related to the risk of hyponatremia

DFF199. Hyponatremia is a complicated condition, the cause of which is multifaceted and incompletely understood. In the most simplistic reductionist terms, hyponatremia can be caused by loss of sodium from the body fluids (i.e., depletional hyponatremia, often caused by diuretic therapy, diarrhea, excessive sweating, or pathological loss of sodium in the urine), or by excess water in the body fluids (i.e., dilutional hyponatremia, usually caused by excess secretion of vasopressin or various drugs). Desmopressin-induced hyponatremia is dilutional because desmopressin acts in the kidney to cause water retention. (*See* DX-36.) [Anticipated testimony of Dr. Verbalis]

DFF200. It is well known that certain populations are at higher risk for hyponatremia, particularly older patients with incidences of 5-7% in the general population and 18-22% in patients in extended care facilities. (*See* DX-39.) [Anticipated testimony of Dr. Verbalis]

DFF201. In considering desmopressin-induced hyponatremia specifically, it is important to recognize that production of dilutional hyponatremia requires two factors:

1) antidiuresis, which is the action of desmopressin in the kidney, and

2) water intake, which is retained by the action of desmopressin and dilutes the sodium concentration to lower levels.

There are several ways in which a treating physician could reduce the risk of hyponatremia associated with the administration of desmopressin, including administering less desmopressin and decreasing fluid intake, but neither of these alone is sufficient to reduce the risk of hyponatremia or even determine that a risk exists. [Anticipated testimony of Dr. Verbalis]

DFF202. The amount of water retained in response to a given dose or route of administration of desmopressin is not directly related to the plasma level or duration of effect of desmopressin. To equate a decreased risk of hyponatremia with a decreased administered dose of desmopressin is overly simplistic and ignores the pathophysiology that causes this adverse effect. Factors for hyponatremia include patient sensitivity to desmopressin (sensitivity of the V2 receptors), blood levels of desmopressin, solutes diuresis, and postural hypertension in the elderly. (DX-11-0001.) [Anticipated testimony of Dr. Verbalis]

DFF203. One must also always consider fluid intake as well as desmopressin administration; even the guidelines for administering various desmopressin dosage forms have long advised that fluid intake should be reduced or moderated. (*See, e.g.,* JX-6-0003 at § 5.1 and JX-5-0004 at § 5.1.) More importantly, as hyponatremia is defined by the level of sodium in the blood, serum sodium monitoring is a prerequisite for determining whether a risk of developing hyponatremia exists and for reducing such a risk. [Anticipated testimony of Dr. Verbalis]

DFF204. As noted above, the common specification provides only general statements regarding hyponatremia. (*See* JX-1-0013 at 2:15-19; JX-1-0020 at 16:29-42.) Only one of the three clinical examples in the patents in suit (Example 8 and not Example 7 or Comparative Example 4) even mentions hyponatremia or serum sodium, and that is also with

only general statements related to a study involving i.v. infusion of desmopressin in healthy subjects. (JX-1-0023 at 21:6-9, 21:17-21.) [Anticipated testimony of Dr. Verbalis]

DFF205. Example 8 does include data for urine osmolality and urine output, but these effects are not solely related to desmopressin (e.g., the subjects were water loaded); there is not a one-to-one correlation between the blood plasma concentration of desmopressin and urine osmolality or urine output. Moreover, these data do not directly correlate to a risk of hyponatremia. One of ordinary skill would understand that using these data as indicators for the risk of hyponatremia fails to account for critical factors impacting serum sodium levels such as fluid intake and variabilities related to desmopressin sensitivity. More importantly, the common specification does not report or even discuss any serum sodium data, which is necessary to assess any risk of hyponatremia or determine whether any dose or dosage form (including the i.v. infusion in Example 8) manifests a reduction of the risk of hyponatremia. [Anticipated testimony of Dr. Verbalis]

DFF206. The only other discussion related to hyponatremia, and the monitoring of serum sodium in particular, is the conclusory statement after Example 8 that "[s]afety and tolerability were excellent." (JX-1-0026 at 27:2-3.) [Anticipated testimony of Dr. Verbalis]

DFF207. The common specification does not provide a sufficient disclosure regarding the claimed methods for reducing the risk of hyponatremia. Serum sodium data would be the minimum disclosure needed by a POSITA to evaluate whether there was a risk of hyponatremia. (*See* JX-1-0022 at 19:19-37, 20:13-25, 20:34-49.) And even more would be needed to show that Dr. Fein actually invented—was in possession of—a method for reducing such a risk while still practicing the claimed methods (of achieving therapeutic efficacy via treating various voiding disorders, inducing voiding postponement, or inducing an antidiuretic

effect), particularly with seemingly limitless combinations of dosage forms, routes of administration, and doses provided in the common specification. (*See, e.g.*, JX-1-0020 to JX-1-0021 to JX-1-022 at 16:46-17:15.) [Anticipated testimony of Dr. Verbalis]

G. The asserted claims are invalid for lack of enablement based on Dr. Fein's admissions in front of the EPO

DFF208. Beyond the patents in suit, Dr. Fein filed additional patent applications directed to desmopressin. For example, Dr. Fein applied for patents in the United States Patent and Trademark Office ("PTO") and European Patent Office ("EPO") directed to a particular nasal spray formulation. From those applications, the PTO issued U.S. Patent No. 9,539,302 ("the '302 patent") and the EPO issued European Patent No. 2442821 (DX-34; "Eur '821 patent"), both of which list Dr. Fein as the sole inventor.

DFF209. The Eur '821 patent is a foreign counterpart of the '302 patent and has a single claim, which is directed to a "composition of matter comprising an intranasal desmopressin dose in the form of a plume ejected over a time interval from the nozzle of a metered dose spray device." (DX-34-0016 at cl. 1.)

DFF210. The Eur '821 patent was subject to an opposition proceeding at the European Patent Office ("EPO"). One of the prior art references cited in the opposition proceeding was the '203 patent, where it was referred to as "D8." (*See* (DX-37-0018 at ¶ 61.)

DFF211. On August 7, 2018, Dr. Fein's representatives in Europe submitted to the EPO on behalf of Serenity a Response to the Notice of Opposition (DX-38) ("Opp'n Response").

DFF212. The Opp'n Response also refers to the '203 patent as "D8." (DX-38.)

DFF213. The Opp'n Response includes the statement:

> D8 is concerned with the problem of improving existing desmopressin formulations in general (without providing specific details), so that they are easy to use for patients and have less side

> effects (e.g. hyponatremia) (See Col. 2, lines 6-22). D8 further mentions that it would be desirable to have lower dosage of desmopressin for treatment of condition such as nocturia (col. 16, lines 25-45).

(DX-38-0043 at ¶ 11.10.)

DFF214. The Opp'n Response also states that:

> [T]he skilled person understands that D8's teaching is centered on sublingual dosage forms. D8 does not explore how to improve formulation nor findings [sic] ways of administering low dose of desmopressin for an intranasal dosage form, which results in low blood concentrations (no more than 15 pg/ml, preferably less than 10 pg/ml), while reducing variability, increasing bioavailability, having therapeutic efficacy (inducing an antidiuretic effects), and reducing the risk of hyponatremia.

(DX-38-0043 at ¶ 11.12.)

DFF215. The Opp'n Response further states:

> With respect to "low dose" desmopressin, D8 teaches the following: The dosages for the sublingual dosage form range between 0.5 ng to 20 mcg, and are said to be effective in establishing a steady plasma/serum desmopressin concentration in the range of from about 0.1 picograms desmopressin per mL plasma/serum to about 10.0 picogram desmopressin per mL plasma/serum (Col. 2, lines 26-37). D8 further teaches preferred (narrower) dosages in col. 4, lines 1-19, including of 0.5 or 1 mcg to 1 mg or 2 mcg to 800 mcg or 10 mcg to 600 mcg per or 0.5 ng to 20 000 ng or 0.05 mcg to 10 mcg or 0.1 mcg to 2 mcg. It is noteworthy that the broader (0.5 ng to 20 mcg) and narrower dosage ranges disclosed in col. 4, lines 1-19 (e.g. 0.1 mcg to 2 mcg) are specific to the sublingual dosage forms and do not apply to intranasal dosage forms.

(DX-38-0043 at ¶ 11.13 (emphasis omitted).)

DFF216. In addition, Opp'n Response states:

> It is noteworthy that the teaching of D8 with respect to the Table in Col. 17 <u>is not enabled</u>, i.e. there is [sic] no examples demonstrating that any of the suggested dose ranges are effective to establish a steady plasma/serum desmopressin concentration in the range of from about 0.1 picograms desmopressin per mL plasma/serum to about 10.0 picogram desmopressin per mL plasma/serum in a

> patient, let alone provide therapeutic efficacy for the conditions indicated above (e.g., inducing an antidiuretic effect for less than about 6 hours, and which lower the risk of hyponatremia).

(DX-38-0044 at ¶ 11.14 (emphasis in original).)

DFF217. The Opp'n Response also states:

> [T]he skilled person would still need to refine (narrow) the broad dose range taught in D8 (0.1 mcg to 20 mcg) to arrive at the dose range of claim 1 (1-5 mcg or 0.75 mcg), and *perform tests to find dosage(s) that are effective* in producing blood levels of not more than 15 ± 3 pg/ml, preferably no more than 10 pg/ml, and show therapeutic efficacy (inducing an antidiuretic effect of about less than 6 hrs), and lead to a lower risk of hyponatremia. *This would amount to a research program*.

(DX-38-0049 at ¶ 11.37 (emphasis added).)

DFF218. On August 30, 2019, the EPO issued a communication concluding that the Eur '821 patent would be revoked. [Anticipated testimony of Dr. Polz, Dr. Fein.]

H. Asserted claims 10, 11, 12, and 13 of the '203 patent are invalid for lack of enablement for the "amount" of desmopressin and the "time sufficient to achieve" the claimed plasma concentrations

DFF219. Each of asserted claims 10, 11, 12, and 13 of the '203 patent require administration of some "amount" of desmopressin "for a time sufficient to establish" a maximum desmopressin plasma concentration. (JX-1-0026 at cl. 10, 11, 12, 13.)

DFF220. There are no restrictions on the absolute dose "amount" of desmopressin administered and each of asserted claims 10, 11, 12, and 13 of the '203 patent encompass formulations that may be administered by transmucosal, transdermal, or intradermal delivery. (JX-1-0026 at cl. 10, 11, 12, 13.) [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

DFF221. The common specification does not disclose any working examples of formulations that meet the pharmacokinetic parameters of asserted claims 10, 11, 12, and 13 of the '203 patent. [Anticipated testimony of Dr. Mayersohn.]

DFF222. Although the common specification discloses routes of administration and effective daily dose ranges in column 17 (JX-1-0021 at 17:1-15), there is no additional information in the common specification to show that these alleged doses for the routes of administration teach or show that the dosages for the routes of administration are, in fact, effective to meet the functional limitations of the asserted claims or to provide therapeutic efficacy over the entire claimed range. [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

DFF223. Further, there is no teaching or disclosure in the common specification of specific formulations (and the bioavailabilities of those formulations) for transmucosal, transdermal, or intradermal routes of administration that are sufficient to achieve the claimed plasma concentrations. Without knowing the bioavailability of a particular formulation, a POSITA cannot know what "amount" of desmopressin is sufficient to achieve the claimed plasma concentrations, regardless of the alleged "effective therapeutic doses" disclosed in column 17 of the common specification. [Anticipated testimony of Dr. Mayersohn.]

DFF224. A POSITA would be faced with a myriad of different potential formulations, which could include (i) different amounts of desmopressin, (ii) different types of excipients; (iii) different amounts of excipients, and (iv) different physical forms (e.g., solid tablet or liquid). [Anticipated testimony of Dr. Mayersohn.]

DFF225. Further, these formulations could result in different types of release. For example, immediate release, controlled release, or delayed release. Each of these different release types and each of the different formulations will affect the time required for desmopressin to be absorbed after administration. [Anticipated testimony of Dr. Mayersohn.]

DFF226. The common specification does not provide any teaching or guidance on the "time sufficient to achieve" the claimed plasma concentrations of desmopressin. [Anticipated testimony of Dr. Mayersohn.]

DFF227. In order to determine if a particular formulation contained an "amount" of desmopressin that would be administered over a "time sufficient to achieve" the required desmopressin plasma concentration, it would be necessary to conduct a clinical trial to build a model of the plasma concentrations over time. [Anticipated testimony of Dr. Mayersohn.]

DFF228. These individual data would allow for modeling of each individual concentration curve and allow the information to be aggregated to help build a predictive model, which could then be used to provide an individual estimate of the plasma concentrations when using a different formulation (e.g., a different dosage form or administration route) or a different study population (e.g., patients rather than healthy volunteers). [Anticipated testimony of Mr. Vis.]

DFF229. Without these data, which are missing from the common specification, it is not possible to extrapolate how another dosage form would work or to extrapolate how any specific individual (much less a patient rather than a healthy volunteer) in another population would react. [Anticipated testimony of Mr. Vis.]

I. The asserted claims of the '321 patent are invalid for lack of enablement for the "no more than about 2 ng/kg" limitation

DFF230. The asserted claims of the '321 patent as they depend from claim 1 each require delivering "no more than about 2 ng/kg" of desmopressin to a patient's bloodstream. (JX-2-0027 to JX-2-0028 at cl. 3, 5, 6, 7, 12.)

DFF231. Based on the clear language of the claims, the claim language encompasses all doses of desmopressin that deliver "no more than about 2 ng/kg" desmopressin to a patient's bloodstream.

DFF232. The asserted claims of the '321 patent are not enabled because the common specification does not teach a POSITA which doses below "about 2 ng/kg" are effective to achieve the claimed antidiuretic effect.

DFF233. Based on the data in Example 8, doses of 0.5 ng/kg delivered to the bloodstream are insufficient to meet the durations of action claimed in the asserted claims of the '321 patent. [Anticipated testimony of Mr. Vis, Dr. Mayersohn.]

DFF234. Based on the data in Example 8 doses of 1.0 ng/kg delivered to the bloodstream were insufficient to meet the durations of action claimed in the asserted claims of the '321 patent in seven of the eight individuals tested in Example 8. [Anticipated testimony of Mr. Vis, Dr. Mayersohn.]

DFF235. Based on the data in Example 8, doses of 2.0 ng/kg delivered to the bloodstream were in some cases insufficient to meet the durations of action claimed in the asserted claims of the '321 patent and in other cases resulted in durations of action that were too long to meet the durations of action claimed in the asserted claims of the '321 patent. [Anticipated testimony of Mr. Vis, Dr. Mayersohn.]

DFF236. Although the common specification discloses routes of administration and effective daily dose ranges in column 17 (JX-1-0021 at 17:1-15), there is no additional information in the common specification (other than conjecture) to show that these alleged doses for the routes of administration teach or show that the dosages for the routes of administration

are, in fact, effective to meet the functional limitations of the asserted claims or to provide therapeutic efficacy. [Anticipated testimony of Dr. Spaans.]

DFF237. Further, there is no teaching or disclosure in the common specification of specific formulations (and the bioavailabilities of those formulations) for intranasal, transdermal, intradermal, transmucosal, or conjunctival routes of administration that are sufficient to deliver "no more than about 2 ng/kg" desmopressin to a patient's bloodstream. Without knowing the bioavailability of a particular formulation and the rates of delivery and elimination, a POSITA cannot know what "amount" of desmopressin is sufficient to achieve desmopressin delivery to the bloodstream, regardless of the alleged "effective therapeutic doses" disclosed in column 17 of the common specification. [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

DFF238. Even relatively small changes in the formulation, however, can affect the bioavailability. As such, for each new dosage form it would be necessary to conduct a clinical trial to determine the bioavailability and thus the resulting plasma concentrations. Even putting aside the sheer volume of tests that would be necessary to gain any understanding concerning the multitude of covered formulations and methods of administration, as noted above, such clinical trials would be neither trivial nor predictable. [Anticipated testimony of Dr. Spaans.]

DFF239. The asserted claims of the '321 patent are broad and cover treatment with an open-ended set of desmopressin formulations that can be administered by five different routes of administration. [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

DFF240. Because of the high inter- and intra- subject variability in pharmacodynamic response, as seen in Example 8, it is not possible to predict how an individual patient will respond to a specific desmopressin formulation without administering the formulation and seeing what happens. [Anticipated testimony of Dr. Spaans, Mr. Vis.]

DFF241. Based on the data in Example 8, doses that deliver less than 1.0 ng/kg will not be effective to treat patients to achieve the required durations of action claimed in the asserted claims of the ’321 patent. In other words, the data in Example 8 show that at least half of the claimed range is not enabled. [Anticipated testimony of Mr. Vis.]

DFF242. Based on the data in Example 8, at least some patients administered doses that deliver 2.0 ng/kg desmopressin to the patient’s bloodstream will exceed the claimed durations of action in the asserted claims of the ’321 patent. Further, based on the data in Example 8, at least some patients administered doses that deliver 2.0 ng/kg desmopressin to the patient’s bloodstream will fall below the claimed durations of action in the asserted claims of the ’321 patent. [Anticipated testimony of Mr. Vis, Dr. Mayersohn.]

DFF243. The common specification does not teach formulations or doses of a formulation that are sufficient to deliver less than about 2.0 ng/kg desmopressin to a patient’s bloodstream while achieving the claimed durations of action, much less over the entire range of “less than about 2.0 ng/kg” desmopressin. [Anticipated testimony of Mr. Vis, Dr. Mayersohn.]

DFF244. The common specification would require a POSITA to perform an iterative, trial-and-error process to develop a formulation for treatment that would meet all the limitations of the asserted claims of the ’321 patent. [Anticipated testimony of Dr. Spaans.]

III. The Asserted Claims of the '321 Patent Are Indefinite under 35 U.S.C. § 112, ¶ 2

DFF245. Asserted claims 6 and 12 of the '203 patent and the asserted claims of the '321 patent are indefinite because a POSITA would not understand the scope of the "about" limitations.

DFF246. Asserted claim 6 of the '203 patent, which depends from unasserted claim 1, requires maintaining a desmopressin plasma concentration within the range of "about" 0.5 pg/ml and 10 pg/ml for "about" four to six hours. (JX-1-0026 at cl. 6.)

DFF247. Asserted claim 12 of the '203 patent, which depends from claim 10, requires establishing a desmopressin plasma concentration of "about" 5 pg/ml. (JX-1-0026 at cl. 12.)

DFF248. The asserted claims of the '321 patent all require that an antidiuretic effect or urine osmolality be maintained for "about" a specific amount of time. (JX-2-0027 to JX-2-0028 at cl. 3, 5, 6, 7, 12.)

DFF249. Counterclaimants' expert Dr. Mayersohn has admitted that the claim requires values that are "close" to the recited values, but has also admitted that he does not know how "close" to the recited values one must be to meet the claim limitations. [Anticipated testimony of Dr. Mayersohn.]

DFF250. Counterclaimants' expert Dr. Mayersohn has also admitted that he does not know if any value outside of the specifically claimed numerical value or numerical range would fall within the scope of asserted claims 6 and 12 of the '203 patent and the asserted claims of the '321 patent. [Anticipated testimony of Dr. Mayersohn.]

IV. If the Court Adopts Dr. Mayersohn's Assumptions Underlying His Infringement Opinions, Claims 10, 11, 12, and 13 of the '203 Patent Are Obvious under 35 U.S.C. § 103

DFF251. Ferring's obviousness arguments are based on the same logic adopted by Counterclaimants' expert, Dr. Mayersohn, in connection with his arguments concerning infringement. Specifically, Dr. Mayersohn opines that a patient's pharmacokinetic response to a given dose of desmopressin can be predicted based on observations concerning the linearity of the relationship between desmopressin dose and pharmacokinetic response based on mean population data. Ferring does not agree that extrapolations concerning such data are appropriate, but to the extent they are accepted, the same logic demonstrates that prior art desmopressin formulations render claims 10, 11, 12, and 13 of the '203 patent obvious. [Anticipated testimony of Dr. Spaans.]

DFF252. A POSITA would recognize that combining Dr. Mayersohn's logic with the information disclosed in the Ferring 1998 Label, in view of the Finnish 2001 Label and Fjellestad-Paulsen (1993), renders claims 10, 11, 12 and 13 of the '203 patent invalid as obvious. [Anticipated testimony of Dr. Spaans.]

A. Summary of the prior art

1. Commercially available formulations

DFF253. Well before May 7, 2002, Ferring sold desmopressin on the market in the U.S. as both a nasal spray and an oral tablet (that you take and swallow with water). (JX-13-0019; JX-1-0014 at 1:22-33 (under "Brief Description of the Related Art," "Desmopressin is commercially available as the acetate salt both in tablet form and as a nasal spray, and is commonly prescribed for voiding postponement, incontinence, primary nocturnal enuresis (PNE)

and nocturia, among other indications, including central diabetes insipidus.")) [Anticipated testimony of Dr. Spaans.]

DFF254. The oral tablet was marketed under the name DDAVP in the United States and MINIRIN in Europe. (JX-13-0014, JX-13-0019.) [Anticipated testimony of Dr. Spaans.]

2. Prior art references

a) Ferring 1998 Label

DFF255. The 1998 package insert for Ferring's DDAVP tablets ("Ferring 1998 Label") was available to the public by March 1998. (DX-1-0002.) [Anticipated testimony of Dr. Spaans.]

DFF256. The Ferring 1998 Label discloses that DDAVP tablets are oral tablets that contain either 0.1 milligram (equivalent to 100 µg) or 0.2 mg (equivalent to 200 µg) desmopressin acetate. (DX-1-0001.) [Anticipated testimony of Dr. Spaans.]

DFF257. The Ferring 1998 Label discloses that DDAVP oral tablets are indicated to treat CDI and PNE. (DX-1-0001.) These tablets have also been prescribed "off-label" to treat nocturia since at least before the priority date of the patents in suit. [Anticipated testimony of Dr. Lowe.]

DFF258. The recommended doses taught by the Ferring 1998 Label differ by indication and patient age. (DX-1-0001.) For central diabetes insipidus, the Ferring 1998 label recommends that "dosing should start at 0.05 mg [50 µg] (1/2 of the 0.1 mg tablet)." (DX-1-0002.) For primary nocturnal enuresis, the Ferring 1998 label recommends the dosage be determined for each individual patient and adjusted according to response. (DX-1-0002.) The recommended initial dose for patients age 6 years and older is 0.2 mg (200 µg) at bedtime, and the dose can be titrated up to 0.6 mg (600 µg) to achieve the desired response. (DX-1-0002.) [Anticipated testimony of Dr. Spaans.]

b) Finnish 2001 Label

DFF259. The Summary of Product Characteristics for Ferring's MINIRIN 0.1 mg (100 µg) tablet ("Finnish 2001 Label") was available to the public by August 9, 2001. (DX-33-0012.) [Anticipated testimony of Dr. Spaans.]

DFF260. The Finnish 2001 Label discloses that MINIRIN tablets are desmopressin oral tablets indicated to treat central diabetes insipidus, primary nocturnal enuresis, and nocturia. (DX-33-0007 to DX-33-0008.) [Anticipated testimony of Dr. Spaans.]

DFF261. The MINIRIN tablets are the same physical tablets as the DDAVP tablets described above with respect to the Ferring 1998 label, just branded differently for sale in Europe as opposed to the U.S. [Anticipated testimony of Dr. Spaans.]

DFF262. For the nocturia indication, the recommended dose is 0.1 mg (100 µg) at bedtime. (DX-33-0008.) [Anticipated testimony of Dr. Spaans.]

c) Fjellestad-Paulsen (1993)

DFF263. The peer-reviewed scientific article "Pharmacokinetics of 1-deamino-8-D-arginine vasopressin after various routes of administration in healthy volunteers" by Fjellestad-Paulsen et al. ("Fjellestad-Paulsen (1993)") was published in the journal Clinical Endocrinology in 1993. (DX-24.) [Anticipated testimony of Dr. Spaans.]

DFF264. Fjellestad-Paulsen (1993) is directed to investigating the pharmacokinetics of desmopressin in healthy adults after intravenous, subcutaneous, intranasal, oral, sublingual and intrarectal administration. (DX-24-0001.) [Anticipated testimony of Dr. Spaans.]

DFF265. Fjellestad-Paulsen (1993) teaches that the C_{max} following subcutaneous administration of 2 µg of desmopressin is 58.3 pmol/l; following intranasal administration of 20 µg of desmopressin is 19.9 pmol/l; and following oral administration of 200 µg of desmopressin is 12.7 pmol/l. (DX-24-0003 (Table 2).) The units pmol/l can be readily converted to pg/ml (the

units used to describe the C_{max} in the asserted claims of the '203 patent) if the molecular weight is known. The molecular weight of desmopressin is 1,069 g/mol. Thus, the C_{max} following oral administration provided by Fjellestad-Paulsen (1993), 12.7 pmol/l, can be converted to a C_{max} of 13.6 pg/ml based on the molecular weight of desmopressin (12.7 pmol/l * 1,069 g/mol * 10^{-12} mol/pmol * 10^{12} pg/g * 10^{-3} l/ml = 13.6 pg/ml). [Anticipated testimony of Spaans.]

DFF266. Fjellestad-Paulsen (1993) describes the desmopressin concentration-time course profile over eight hours following intravenous, subcutaneous, intranasal, and oral administration. (DX-24-0003 (Figure 3).) After all routes of administration, with the exception of intrarectal, an effect on urine osmolality was observed. (DX-24-0005.) [Anticipated testimony of Dr. Spaans.]

3. Motivation to combine the prior art references

DFF267. A POSITA would recognize that there would be motivation to combine the teachings from the Ferring 1998 Label, the Finnish 2001 Label, and Fjellestad-Paulsen (1993) so as to arrive at the claimed invention. [Anticipated testimony of Dr. Spaans.]

DFF268. As noted above, the oral tablets described in the Ferring 1998 Label and the Finnish 2001 Label are the same physical tablets. (DFF261.) As described above, a POSITA would be a team of individuals, including at least an individual with an advanced degree (e.g., a Ph.D. or Master's or PharmD or equivalent) in one of the pharmaceutical sciences and three to five years of experience in clinical pharmacology or drug formulation. (DFF76) Such an individual would be motivated to consult and combine the teachings of multiple references concerning known formulations of desmopressin, especially where those references concern the same physical formulations.

DFF269. Similarly, the oral tablets tested in Fjellestad-Paulsen (1993) are the same physical tablets described in the Ferring 1998 Label and the Finnish 2001 Label. (DX-24-0002, DX-24-0005.) [Anticipated testimony of Dr. Spaans.] Thus, a POSITA would be motivated to consult and combine Fjellestad-Paulsen (1993) with both labels when considering the administration of the oral tablets described therein. As described above, a POSITA would be a team of individuals, including at least an individual with an advanced degree (e.g., a Ph.D. or Master's or PharmD or equivalent) in one of the pharmaceutical sciences and three to five years of experience in clinical pharmacology or drug formulation. (DFF76.) Such an individual would be motivated to consult and combine the teachings of multiple references concerning known formulations of desmopressin, especially where those references concern the same physical formulations. [Anticipated testimony of Dr. Spaans.

B. If the Court adopts the assumptions underlying Dr. Mayersohn's infringement analysis, the combination of the Ferring 1998 Label, the Finnish 2001 Label, and Fjellestad-Paulsen (1993) renders claims 10, 11, 12, and 13 of the '203 patent invalid as obvious

DFF270. It was known before the earliest possible priority date of the '203 patent that even low concentrations of desmopressin had a potent antidiuretic effect and could mitigate the risk of hyponatremia. [Anticipated testimony of Dr. Nørgaard.]

DFF271. It was also known that higher doses of desmopressin could produce a longer antidiuretic effect, increasing the risk of hyponatremia. This recognition formed the basis of Ferring's desmopressin development. [Anticipated testimony of Dr. Nørgaard.]

1. The "method" limitations of claims 10, 11, 12, and 13

DFF272. Claim 10 of the '203 patent (and claims 11 and 12 through their dependence on claim 10) requires "[a] method for inducing an antidiuretic effect in a patient

comprising the step of administering to a patient a pharmaceutical composition comprising desmopressin." (JX-1-0026 at cl. 10, 11, 12.) Claim 11 is further limited to "patient[s] suffering from incontinence, primary nocturnal enuresis (PNE), or nocturia." (JX-1-0026 at cl. 11.) Similarly, claim 13 requires "[a] method for treating a patient suffering from nocturia comprising administering to a patient a pharmaceutical composition comprising desmopressin." (JX-1-0026 at cl. 13.)

DFF273. The Ferring 1998 Label discloses administration of a pharmaceutical composition comprising desmopressin, i.e., the oral desmopressin tablet, to treat central diabetes insipidus and primary nocturnal enuresis. (DX-1-0001.) [Anticipated testimony of Dr. Spaans.]

DFF274. The Finnish 2001 Label discloses administration of a pharmaceutical composition comprising desmopressin, i.e., the oral desmopressin tablet, to treat central diabetes insipidus, primary nocturnal enuresis, and nocturia. (DX-33-0007 to DX-33-0008 at 7-8.)

DFF275. The goal in treating each of CDI, PNE, and nocturia is to produce an antidiuretic effect. [Anticipated testimony of Dr. Verbalis.] Additionally, the use of desmopressin to treat primary nocturnal enuresis and nocturia are explicitly disclosed in the references. Thus, the Ferring 1998 Label and the Finnish 2001 Label, alone or in combination, teach the general methods of use required by each of claims 10, 11, 12, and 13 of the '203 patent.

2. The "transmucosal delivery" limitations of the asserted claims

DFF276. Each of claims 10, 11, 12, and 13 of the '203 patent can be practiced by delivering desmopressin via "transmucosal . . . delivery." (JX-1-0026 at cl. 10, 11, 12, and 13.) [Anticipated testimony of Dr. Spaans.]

DFF277. As noted above, the Court construed "transmucosal . . . delivery" appearing in claims 10 and 13 of the '203 patent as "delivering desmopressin by way of a

mucosal tissue, such as the sublingual mucosa." (DFF35.) Thus, transmucosal delivery, as construed by the Court, includes delivery by way of any mucosal tissue, including the mucosa in the mouth and gastrointestinal tract. Accordingly, the use of oral tablets to administer desmopressin results in transmucosal delivery. (*See* JX-1-0021 at 17:1-15.) [Anticipated testimony of Dr. Mayersohn.]

DFF278. Each of the Ferring 1998 Label, the Finnish 2001 Label, and Fjellestad-Paulsen (1993) concern the administration of desmopressin using at least oral tablets. Thus, these references, alone or in combination, teach administration of desmopressin using "transmucosal . . . delivery," as required by claims 10, 11, 12, and 13 of the '203 patent.

3. The "plasma concentration" limitations of the asserted claims

DFF279. The only remaining limitations of claims 10, 11, 12, and 13 all relate to achieving certain plasma concentrations through the administration of desmopressin, i.e., administering the desmopressin "in an amount and for a time sufficient to establish a maximum serum/plasma desmopressin concentration no greater than 10 pg/ml" (claims 10, and 11), "in an amount and for a time sufficient to establish a maximum serum/plasma desmopressin concentration greater than 0.1 pg/ml and less than 10 pg/ml" (claim 13), or "in an amount and for a time sufficient to establish a serum/plasma desmopressin concentration no greater than about 5 pg/ml" (claim 12). (JX-1-0026 at cl. 10, 11, 12, 13.)

DFF280. Dr. Mayersohn's infringement opinions assume that linearity exists between desmopressin dose and plasma concentration, even for doses for which linearity has not been tested and/or demonstrated. [Anticipated testimony of Dr. Spaans.] Specifically, even though Counterclaimants have not tested patients that have taken NOCDURNA® orodispersible tablets to assess the resulting desmopressin plasma concentrations, Dr. Mayersohn assumes that

test results based on other (higher) doses of orodispersible tablets (in different populations) can be used to extrapolate desmopressin plasma concentrations that would result from the administration of 25 µg and 50 µg doses of NOCDURNA® to patients suffering from nocturia. [Anticipated testimony of Dr. Mayersohn, Dr. Spaans.]

DFF281. Additionally, in support of Dr. Mayersohn's opinion that there is written description for the vast formulations and methods of administration covered by the asserted claims of the '203 patent—and that the use of those formulations and methods of administration are enabled—Dr. Mayersohn also assumes that different formulations' relative bioavailabilities can be used to determine equivalent doses that would produce the same desmopressin plasma concentrations for different formulations. [Anticipated testimony of Dr. Mayersohn, Dr. Spaans.] In doing so, Dr. Mayersohn expands his assumptions about dose/response linearity to not only doses beyond the dose range actually tested, but also to all desmopressin formulations covered by the claims. Without this assumption, Dr. Mayersohn cannot demonstrate that the asserted claims of the patents in suit are sufficiently described by or enabled by the common specification. [Anticipated testimony of Dr. Spaans.]

DFF282. If Dr. Mayersohn's assumptions are accepted by the Court (i.e., if the Court finds the asserted claims of the '203 patent have sufficient written description support, are enabled, and are infringed), then claims 10, 11, 12, and 13 of the '203 patent are rendered obvious by the combination of the Ferring 1998 Label, the Finnish 2001 Label, and Fjellestad-Paulsen (1993). [Anticipated testimony of Dr. Spaans.]

DFF283. As noted above, Fjellestad-Paulsen (1993) concerns studies conducted with Ferring's prior art oral desmopressin tablets (described in at least the Ferring 1998 Label). It reports a C_{max} of 12.7 pmol/L following administration of the 200 µg tablet, which corresponds

to a C_{max} of 13.6 pg/ml for the 200 µg tablet once the units are converted to correspond with those used in the claims of the '203 patent. (DX-24-0003 (*see* Table 2).) [Anticipated testimony of Dr. Spaans.]

DFF284. According to Dr. Mayersohn's assumptions regarding desmopressin dose/plasma concentration linearity, this result demonstrates that administration of the 100 µg prior art oral tablet (one-half of the tested 200 µg tablet) would result in a C_{max} of 6.8 pg/ml (one-half of the observed C_{max} for the 200 µg tablet). Both the Ferring 1998 label and the Finnish 2001 Label disclose treating patients with the oral tablet using a 100 µg dose. [Anticipated testimony of Dr. Spaans.]

DFF285. The Ferring 1998 Label also discloses administration of desmopressin to patients suffering from central diabetes insipidus in doses as low as 50 µg, which according to Dr. Mayersohn's assumptions regarding dose/response linearity would result in a C_{max} of 3.4 pg/ml. [Anticipated testimony of Dr. Spaans.] Claim 12 is the only asserted claim of the '203 patent that is limited to a C_{max} "no greater than about 5 pg/ml" (as opposed to 10 pg/ml). The method of claim 12 is not limited by the treatment of a particular indication, requiring only ""[a] method for inducing an antidiuretic effect." (JX-1-0026 at cl. 12.) Because the goal in treating central diabetes insipidus is to produce an antidiuretic effect, the disclosures of the Ferring 1998 Label regarding the treatment of that condition are relevant to this limitation. [Anticipated testimony of Dr. Verbalis.]

DFF286. Thus, these references, alone or in combination, teach the "plasma concentration" limitations of asserted claims 10, 11, and 13 (not greater than 10 pg/ml and/or between 0.1 pg/ml and 10 pg/ml) and claim 12 (not greater than 5 pg/ml) of the '203 patent. [Anticipated testimony of Dr. Spaans.]

C. Counterclaimants have failed to show that the secondary considerations of nonobviousness are sufficient to overcome the finding of obviousness

1. Long-felt need and failure of others

DFF287. With respect to long-felt need/failure of others, Counterclaimants' expert Dr. Mayersohn has opined that "there was a long felt but unmet need for a desmopressin product that achieved lower plasma/serum concentrations with a reduced duration of action" and "the evidence suggests that at the time of Dr. Fein's invention the trend in the industry was to increase the dose of desmopressin – and as a result the plasma concentration – rather than to lower the dose and the concentration." However, as demonstrated below, it was Dr. Nørgaard, not Dr. Fein, who recognized that Ferring should shift to low doses resulting in low plasma concentrations of desmopressin, rather than pursue higher doses. Dr. Nørgaard further recognized that increased exposure extends duration of action. These discoveries were made before Dr. Fein's alleged oral conversation with Ron Nardi in August 2001 where Dr. Fein claims to have conveyed these ideas to Dr. Nardi. [Anticipated testimony of Dr. Fein, Dr. Mayersohn, Dr. Nørgaard.]

2. Unexpected results

DFF288. With respect to unexpected results, Counterclaimants' expert Dr. Mayersohn has opined that he "agree[s] with the Examiner during re-examination of the '203 patent that Dr. Fein's invention is unexpected. In particular, Dr. Fein discovered that by keeping Cmax concentration below 10 pg/ml, it was possible to separate the known anti-diuretic effect of desmopressin from its hyponatremia side effect by reducing the duration of action." Dr. Mayersohn goes on to state, "Based on the studies reported in Example 8 of the specification, Dr. Fein was able to establish that a much lower concentration of desmopressin was sufficient to achieve an antidiuretic effect for a shorter period of time." However, as shown above, Example 8

does not actually support a duration of action of 4 to 6 hours. [Anticipated testimony of Dr. Fein, Dr. Mayersohn, Mr. Vis.]

V. The Patents in Suit Are Invalid under 35 U.S.C. § 102(f) Because Dr. Fein Did Not Himself Invent the Subject Matter Sought to be Patented

A. Dr. Fein's alleged invention as claimed in the patents in suit

DFF289. In the *Ferring v. Allergan* trial (No. 12-cv-2650) ("the 2012 action"), Dr. Fein testified that he conveyed his discoveries regarding desmopressin to Ron Nardi in an oral conversation in August 2001. He claims to have explained to Dr. Nardi that his invention was two-fold:

> Firstly, that desmopressin was more potent and that lower doses would be appropriate particularly for this new clinical indication of nocturia in an elderly population where you wanted to confine the drug effect to just the nighttime hours, four to six hours, at most eight hours, and having that effect dissipate before the patient awakened in the morning and began drinking fluids, coffee, tea, juice. But in order to use a low dose, the oral route of administration was not very suitable because desmopressin is a peptide, meaning it's a small protein. Proteins and peptides get digested when taken orally, and so I knew from the literature that the average bioavailability of the oral desmopressin tablet was .12 percent, meaning on average only about 1/800th of the drug in the tablet got absorbed into the bloodstream, but that could vary tenfold or greater from dose to dose and patient to patient, and the variability was just as bad as the high dose, because you just could not predict what the blood level would be after a given dose and how long the antidiuretic effect would last.
>
> So, I said this new dosage form, the orodispersible tablet, provides an opportunity to avoid the oral route of administration if it were adapted to be placed under the tongue. That's called a sublingual route of administration, and what it means is that the drug is dissolving and being directly absorbed into the bloodstream through the capillary bed under the tongue. That's a type of what is called transmucosal route of administration or transmucosal absorption.

[Anticipated testimony of Dr. Fein]

DFF290. Dr. Fein further testified that he filed his own patent application in the U.S. on May 6, 2003 (PCT '463) for "capturing the low dose invention and a broadened version of the sublingual invention. It included other routes of administration, and it specifically

mentioned transmucosal, of which sublingual is a particular iteration." [Anticipated testimony of Dr. Fein]

DFF291. Dr. Fein has admitted his invention requires sublingual absorption, but the patents in suit do not claim sublingual absorption. [Anticipated testimony of Dr. Fein]

DFF292. Rather, certain claims are independent of route of administration, while other claims recite:

- "administering said composition by transmucosal, transdermal, or intradermal *delivery*" (JX-1-0026 at cl. 2 (emphasis added));
- "administering said composition by" a particular route of *delivery*: intravenous, subcutaneous, transmucosal, transdermal, and intradermal, respectively (JX-1-0026 at cl. 4-8 (emphasis added));
- "administering to a patient a pharmaceutical composition comprising desmopressin by transmucosal, transdermal, or intradermal *delivery*" (JX-1-0026 at cl. 10 (emphasis added));
- "administering to a patient a pharmaceutical composition comprising desmopressin by transmucosal, transdermal, or intradermal *delivery*" (JX-1-0026 at cl. 13 (emphasis added));
- "*delivering* to the bloodstream of the patient an amount of desmopressin no more than about 2 ng/kg by intranasal, transdermal, intradermal, transmucosal, or conjunctival administration" (JX-2-0027 at cl. 1 (emphasis added));
- "administering the desmopressin by" a particular route of *delivery*: intranasal, transdermal, intradermal, transmucosal, and conjunctival, respectively (JX-2-0027 to JX-2-0028 at cl. 9-13 (emphasis added));
- "*delivering* to the bloodstream of the patient via transdermal, intradermal, transmucosal, or conjunctival administration" (JX-2-0028 at cl. 19 (emphasis added)); and
- "*delivering* to the bloodstream of the patient via intranasal administration" (JX-2-0028 at cl. 20 (emphasis added)).

DFF293. The Court construed "transmucosal," appearing in claims 2, 6, 10, and 13 of the '203 patent and in claims 1, 12, and 19 of the '321 patent, as "delivering desmopressin by way of a mucosal tissue, such as the sublingual mucosa." (D.I. 421 at 17.)

DFF294. The Court construed "transmucosal delivery" or "transmucosal . . . delivery," appearing in claims 2, 6, 10 and 13 of the '203 patent as "delivering desmopressin by way of a mucosal tissue, such as the sublingual mucosa." (D.I. 421 at 19.)

DFF295. The Court construed "delivering to the bloodstream . . . by [via] transmucosal . . . administration," appearing in claims 1 and 19 of the '321 patent, as "administering desmopressin by way of a mucosal tissue, such as the sublingual mucosa." (D.I. 421 at 21.)

DFF296. The Court construed "transmucosal administration" or "administering . . . by transmucosal administration," appearing in claim 12 of the '321 patent, is construed as "administering desmopressin by way of a mucosal tissue, such as the sublingual mucosa." (D.I. 421 at 21.)

DFF297. The Court explicitly stated that "'delivery' of desmopressin need not involve actual absorption." (D.I. 421 at 18.)

DFF298. Without claiming sublingual absorption in the patents in suit, Dr. Fein's alleged invention as embodied in the claims is limited to his "low dose invention. [Anticipated testimony of Dr. Fein]

DFF299. Dr. Fein's alleged "low dose invention" is (broadly) claimed in the patents in suit, but there is no evidence that Dr. Fein conceived of the "low dose invention." Instead, Dr. Fein's alleged "low dose invention" as claimed in the patents in suit was based on discoveries Dr. Jens Peter Nørgaard made and the work Dr. Nørgaard did with Thomas Senderovitz in

determining appropriate doses for the orodispersible formulation of desmopressin that Ferring was developing. The additional limitations in the claims of the patents in suit are not inventive aspects of the claims.

DFF300. As of 1999, Dr. Nørgaard was the Head of Clinical Research in Urology at Ferring and was the clinical expert on desmopressin. He was responsible for designing the clinical development program for desmopressin. Dr. Senderovitz was Associate Head of Clinical Pharmacology at Ferring and was responsible for the early clinical development work for the orodispersible formulation.

1. The claims of the '203 patent

DFF301. The '203 patent has fifteen claims. All are method claims. Independent claim 1 of the '203 patent recites:

> 1. A method of treating nocturia, primary nocturnal enuresis, or incontinence, or for inducing voiding postponement, said method comprising administering to a patient in need thereof a pharmaceutical composition comprising a dose of desmopressin sufficient to achieve a maximum desmopressin plasma/serum concentration no greater than 10 pg/ml and maintaining the concentration within the range of about 0.5 pg/ml and 10 pg/ml for about four to six hours.

(JX-1-0026 at cl. 1.)

DFF302. Claim 2 depends from claim 1, and includes the additional recitation of "administering said composition by transmucosal, transdermal, or intradermal delivery." (JX-1-0026 at cl. 2.) Claims 4-8 each also depend from claim 1 and each includes an additional recitation of "administering said composition by" a particular route of delivery: intravenous, subcutaneous, transmucosal, transdermal, and intradermal, respectively. (JX-1-0026 at cl. 4-8.)

DFF303. Claim 3 depends from claim 1 and includes the additional recitation of "treating nocturia." (JX-1-0026 at cl. 3.)

DFF304. Claim 9 depends from claim 1 and includes the additional recitation of "wherein the desmopressin plasma/serum concentration is maintained at a level no greater than about 5 pg/ml." (JX-1-0026 at cl. 9.)

DFF305. Independent claim 10 of the '203 patent recites:

> 10. A method for inducing an antidiuretic effect in a patient comprising the step of administering to a patient a pharmaceutical composition comprising desmopressin by transmucosal, transdermal, or intradermal delivery in an amount and for a time sufficient to establish a maximum serum/plasma desmopressin concentration no greater than 10 pg/ml.

(JX-1-0026 at cl. 10.)

DFF306. Claim 11 depends from claim 10 and includes the additional recitation of "wherein said patient is suffering from incontinence, primary nocturnal enuresis (PNE), or nocturia." (JX-1-0026 at cl. 11.)

DFF307. Claim 12 depends from claim 10 and includes the additional recitation of "wherein said desmopressin pharmaceutical composition is administered in an amount and for a time sufficient to establish a serum/plasma desmopressin concentration no greater than about 5 pg/ml." (JX-1-0026 at cl. 12.)

DFF308. Independent claim 13 of the '203 patent recites:

> 13. A method for treating a patient suffering from nocturia comprising administering to a patient a pharmaceutical composition comprising desmopressin by transmucosal, transdermal, or intradermal delivery in an amount and for a time sufficient to establish a maximum serum/plasma desmopressin concentration greater than 0.1 pg/mL and less than 10 pg/ml.

(JX-1-0026 at cl. 13.)

DFF309. Claim 14 depends from claim 13 and includes the additional recitation of "wherein said the patient is a human or other mammalian subject." (JX-1-0026 at cl. 14.)

DFF310. Claim 15 depends from claim 13 and includes the additional recitation of "wherein said concentration is maintained greater than 0.1 pg/ml for a time greater than 4 hours." (JX-1-0026 at cl. 15.)

2. The claims of the '321 patent

DFF311. The '321 patent has twenty-one claims. All are method claims. Independent claim 1 of the '321 patent recites:

> 1. A method for inducing voiding postponement in a patient while reducing the risk that the patient develops hyponatremia comprising delivering to the bloodstream of the patient an amount of desmopressin no more than about 2 ng/kg by intranasal, transdermal, intradermal, transmucosal, or conjunctival administration, said amount being therapeutically effective to produce an antidiuretic effect lasting for no more than between about 4 and about 6 hours.

(JX-2-0027 at cl. 1.)

DFF312. Claim 2 depends from claim 1 and includes the additional recitation of "delivering to the bloodstream of the patient an amount of desmopressin no more than about 1 ng/kg." (JX-2-0027 at cl. 2.)

DFF313. Claim 3 depends from claim 1 and includes the additional recitation of "advising a patient that fluid intake should be restricted after administration." (JX-2-0027 at cl. 3.)

DFF314. Claim 4 also depends from claim 1 and includes the additional recitation of "advising the patient that no water should be taken after administration." (JX-2-0027 at cl. 4.)

DFF315. Claim 5 depends from claim 1 and includes the additional recitation of "administering desmopressin to a patient suffering from nocturia, primary nocturnal enuresis (PNE), or incontinence." (JX-2-0027 at cl. 5.)

DFF316. Claim 6 depends from claim 1 and includes the additional recitation of "wherein the method produces a plasma/serum desmopressin concentration in the patient of a maximum of no more than about 10 pg/ml." (JX-2-0027 at cl. 6.)

DFF317. Claim 7 also depends from claim 1 and includes the additional recitation of "wherein the method produces a plasma/serum desmopressin concentration in the patient of a maximum of no more than about 5 pg/ml." (JX-2-0027 at cl. 7.)

DFF318. Independent claim 8 of the '321 patent recites:

> 8. A method for inducing voiding postponement comprising administering to a patient an amount of desmopressin sufficient to produce in the patient a urine osmolality ranging above about 300 mOsm/kg for less than about 5 hours after administration.

(JX-2-0027 at cl. 8.)

DFF319. Claims 9-13 each depend from claim 1 or claim 8, and include the additional recitation of "administering the desmopressin by" a particular route of delivery: intranasal, transdermal, intradermal, transmucosal, and conjunctival, respectively. (JX-2-0027 to JX-2-0028 at cl. 9-13.)

DFF320. Claim 14 depends from claim 1 or claim 8, and includes the additional recitation of "administering to the patient between 100 and 2000 ng (0.1 µg to 2 µg) desmopressin." (JX-2-0028 at cl. 14.)

DFF321. Claim 15 depends from claim 8 and includes the additional recitation of "wherein the method produces a plasma/serum desmopressin concentration in the patient no more than about 10 pg/ml." (JX-2-0028 at cl. 15.)

DFF322. Claim 16 also depends from claim 8 and includes the additional recitation of "wherein the method produces a plasma/serum desmopressin concentration in the patient no more than about 5 pg/ml." (JX-2-0028 at cl. 16.)

DFF323. Claim 17 depends from claim 8 and includes the additional recitation of "delivering to the bloodstream of the patient no more than about 2 ng/kg desmopressin." (JX-2-0028 at cl. 17.)

DFF324. Claim 18 depends from claim 8 and includes the additional recitation of "delivering desmopressin to the bloodstream of a patient suffering from nocturia, PNE, or incontinence." (JX-2-0028 at cl. 18.)

DFF325. Independent claim 19 of the '321 patent recites:

> 19. A method for inducing voiding postponement in a patient while reducing the risk that the patient develops hyponatremia comprising delivering to the bloodstream of the patient via transdermal, intradermal, transmucosal, or conjunctival administration no more than about 1 ng/kg desmopressin to produce an antidiuretic effect for no more than about four to about six hours.

(JX-2-0028 at cl. 19.)

DFF326. Independent claim 20 of the '321 patent recites:

> 20. A method for inducing voiding postponement in a patient while reducing the risk that the patient develops hyponatremia comprising delivering to the bloodstream of the patient via intranasal administration no more than about 2 ng/kg desmopressin so as to produce an antidiuretic effect.

(JX-2-0028 at cl. 20.)

DFF327. Claim 21 depends from claim 20 and includes the additional recitation of "delivering to the bloodstream of the patient no more than about 1 ng/kg desmopressin." (JX-2-0028 at cl. 21.)

B. The relevant time frame for conception

DFF328. Dr. Fein has testified that he had conversations with Dr. Nardi about desmopressin in July 2001, but Dr. Fein did not describe his invention to Dr. Nardi during those conversations. [Anticipated testimony of Dr. Fein.]

DFF329. Dr. Fein's first alleged disclosure of his alleged inventive concepts to Dr. Nardi was in August 2001. [Anticipated testimony of Dr. Fein]

DFF330. Ferring filed its GB application on May 7, 2002. (JX-3.)

DFF331. Dr. Fein, through his counsel, then filed PCT '463 on May 6, 2003, wherein he added disclosures directed to low doses and low plasma concentrations of desmopressin and claimed priority to the GB application. (JX-4.) [Anticipated testimony of Dr. Fein]

DFF332. Dr. Fein, through his counsel, then filed the '100 application as a continuation-in-part of PCT '463 on November 12, 2003, where he added Example 8 and Figures 1-9 and claimed priority to PCT '463 and the GB application. (JX-9-0005 to JX-9-0054.) [Anticipated testimony of Dr. Fein]

DFF333. The relevant time points for conception are (i) what occurred before Dr. Fein's alleged oral conversation with Dr. Nardi in August 2001; (ii) the filing of Ferring's GB application on May 6, 2002; (iii) the filing of Dr. Fein's PCT '463 application on May 7, 2003; and (iv) and the filing of Dr. Fein's '100 application on November 12, 2003.

C. Dr. Nørgaard and Dr. Senderovitz together conceived of the alleged invention claimed in the patents in suit

DFF334. Extensive contemporaneous documentation establishes that Dr. Nørgaard and Dr. Senderovitz conceived of the idea that low doses of desmopressin and resulting low plasma levels of desmopressin lead to sufficient antidiuresis, and shorter duration of action, which could decrease the risk of hyponatremia. This was long before Dr. Fein claims to have communicated these general concepts to Dr. Nardi in an oral conversation in August of 2001. [Anticipated testimony of Dr. Nørgaard]

DFF335. Additional documentation after August 2001 further establishes that Dr. Nørgaard and Dr. Senderovitz, not Dr. Fein, conceived of the "low dose invention" claimed in the patents in suit. [Anticipated testimony of Dr. Juul, Dr. Nørgaard]

1. Pre-August 2001 activities

a) Dr. Nørgaard's 1996 Article

DFF336. In 1996, Dr. Nørgaard published an article titled, *"Hyponatremia in Patients with Nocturnal Enuresis Treated with DDAVP"* (DX-2; "1996 article") that discounted the use of higher doses of desmopressin because "[h]igher doses of DDAVP prolong the duration of pharmacologic action and might increase the risk of water intoxication," or hyponatremia. (DX-2-0003.) [Anticipated testimony of Dr. Nørgaard]

DFF337. DDAVP refers to desmopressin and water intoxication refers to hyponatremia. [Anticipated testimony of Dr. Nørgaard]

b) Dr. Nørgaard's 1999 Article

DFF338. In 1999, Dr. Nørgaard published an article on the PK/PD effects of the oral tablet form of desmopressin in which he noted that "even poor absorption of desmopressin may be sufficient to obtain the required level of plasma desmopressin" because it was a "very potent drug." (DX-3-0002.) The article did not posit increased bioavailability at lower doses, but rather stated "I do not think increasing the availability of desmopressin is necessary" and that "it is good that there is a rather bad bioavailability of desmopressin" because increasing the amount in the blood would increase the duration of antidiuretic effect, which was not a desired outcome. (DX-3-0003.) [Anticipated testimony of Dr. Nørgaard]

DFF339. In the conclusion of the article, Dr. Nørgaard stated that "[s]mall plasma concentrations of desmopressin or AVP are required; even poor absorption of desmopressin may

be sufficient to obtain the required level of plasma desmopressin." (DX-3-0002.) He further stated, "Some patients may still experience a wet bed despite maximal antidiuretic effect of desmopressin, and increasing the dosage could result in no clinical effect, but instead may increase the risk of an undesired increase in duration of action." (DX-3-0002.) [Anticipated testimony of Dr. Nørgaard]

DFF340. He also noted in the article that he considered desmopressin to be a very potent drug which acts for a long time and that increasing the uptake would only result in increased duration of action:

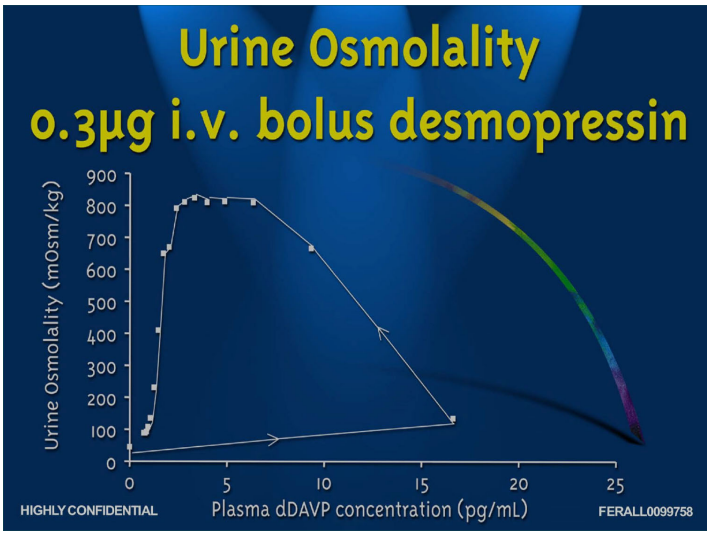
> Desmopressin is a very potent drug and it acts for a long time so I do not think increasing the availability of desmopressin is necessary. In fact, with respect to this, I think it is good that there is a rather bad bioavailability of desmopressin. If you increase the peak uptake of desmopressin it probably does not give you any better clinical response immediately, but it increases the duration of action.

(DX-3-0003.) [Anticipated testimony of Dr. Nørgaard]

c) Dr. Nørgaard's 1999 ICCS Presentation Slides

DFF341. That same year, Dr. Nørgaard gave a presentation at an International Children's Continence Society conference in Denver, Colorado, during which Dr. Nørgaard showed that desmopressin has a maximal antidiuretic effect at far lower plasma concentrations than were previously thought to be clinically effective—as low as 2-3 pg/mL. (DX-4-0012.) [Anticipated testimony of Dr. Nørgaard]

DFF342. The presentation included a slide with a graph (a hysteresis curve) that reflects the relationship between plasma concentration of desmopressin and antidiuretic effect, as shown by urine osmolality (i.e., urine concentration):



(DX-4-0012.) As shown in the graph starting in lower left corner at zero, the 0.3 µg of desmopressin was administered intravenously into a healthy volunteer and (following the arrow on the graph pointing to the right) the plasma concentration immediately rose to the C_{max} around 16 pg/mL. At that point, there was a slow increase in the urine osmolality as the kidneys begin to react (following the arrow up and back to the left), then a continued effect of desmopressin on urinary osmolality of 800-900 mOsm/kg all the way down to plasma concentrations of approximately 3 pg/mL. After that, the urine osmolality dropped, and the individual started producing urine again. The leveling off of the urine osmolality at a maximum effect of just more than 800 mOsm/kg—a level at which it remained until the plasma concentration decreased below about 3 pg/ml—is significant in that that it shows that very low plasma concentrations result in a strong antidiuretic effect with a very high concentration of urine. [Anticipated testimony of Dr. Nørgaard]

DFF343. In the speaking notes that accompanied the presentation, Dr. Nørgaard explained that that the urine concentration remained high "until plasma levels were down to approximately 3 pg/mL, which indicates that very, very low plasma levels of desmopressin are actually needed for high urine concentration ability in the kidneys or – in other words –

sensitivity to desmopressin in healthy volunteers is extremely high." (DX-5-0002.) [Anticipated testimony of Dr. Nørgaard]

DFF344. Based on these data, Dr. Nørgaard concluded in his slides that "[t]he need for high plasma levels of desmopressin is overestimated." (DX-4-0021.) [Anticipated testimony of Dr. Nørgaard]

d) The 45A07-39 Study—December 1999

DFF345. While the individuals in Dr. Nørgaard's ICCS presentation were healthy volunteers, Dr. Nørgaard and Dr. Senderovitz also evaluated plasma concentrations in elderly patients around the same time frame in a study called 45A07-39. (DX-6.) It was a study of bioavailability and pharmacokinetics of desmopressin in elderly men aged 55-75 years, and it showed that a dose of desmopressin in the elderly resulting in a plasma level of 4-5 pg/mL achieved maximum antidiuretic effect. [Anticipated testimony of Dr. Nørgaard]

DFF346. On page FERALL0038593 of the final report, dated December 16, 1999, a graph presented the plasma concentration over time for administration of desmopressin both during daytime (morning) and at nighttime (evening). (DX-6-0032.) The dose was a single 200 µg MINIRIN oral tablet, but it was very poorly absorbed by the patients (who represented a target population for nocturia). The study demonstrated that, in general, very low plasma concentrations and associated low doses of oral desmopressin are expected to be sufficient for the desired clinical response: antidiuresis for the number of hours related to sleep. [Anticipated testimony of Dr. Nørgaard]

DFF347. In the pharmacokinetic and pharmacodynamics conclusions of the study report, Dr. Nørgaard and Dr. Senderovitz explained that the oral administration of 200 µg desmopressin generated the same antidiuretic effect as a much smaller i.v. administration of

desmopressin, and those levels remained "identical" for about six hours. (DX-6-0039.) This demonstrated that an essentially maximum antidiuretic effect was being reached with plasma levels as low as 4 pg/mL, which was in line with the hysteresis curve from Dr. Nørgaard's ICCS presentation. (DX-6-0057 (reporting maximum mean plasma concentration of 4.42 pg/mL for nighttime administration of 200 µg oral tablet).) [Anticipated testimony of Dr. Nørgaard]

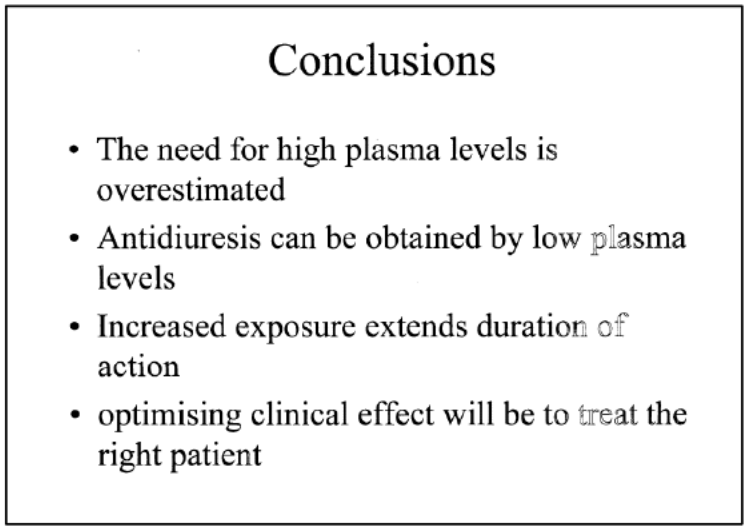
e) Dr. Nørgaard's Rollover Presentation—Early 2000

DFF348. Thereafter, in early 2000 (before Dr. Fein was involved at the desmopressin project at Ferring), Dr. Nørgaard gave an internal presentation to senior management at Ferring with the title "The Minirin rollover." (DX-1.) A "rollover" is a Danish expression meaning that when you completely change your strategy, you make a "rollover." The idea behind this presentation was that Ferring needed to make a radical change in the way forward with desmopressin products. [Anticipated testimony of Dr. Nørgaard]

DFF349. At that time, a thinking existed in the PNE community (including some individuals at Ferring) that if a PNE patient did not respond to desmopressin, the dose should simply be increased. In Dr. Nørgaard's view, this was not the solution; other factors could cause the patients not to respond to desmopressin, which factors should be further investigated to be able to solve the problem of non-responders. It was clear to Dr. Nørgaard that increasing the dosages would not solve that problem. [Anticipated testimony of Dr. Nørgaard]

DFF350. Dr. Nørgaard's rollover theory was that Ferring should shift to low doses resulting in low plasma concentrations of desmopressin, rather than pursue high doses. Specifically, in his presentation, Dr. Nørgaard included Figure 1 from his 1999 paper on non-responders; the hysteresis curve from his ICCS presentation, showing that maximal antidiuresis occurs even at plasma concentrations as low as 3 pg/mL; and the information from the 45A07-39

study, showing the maximum plasma concentrations below 5 and 10 pg/mL, as well as the duration of action being six hours. (DX-7-0006, DX-7-0007, DX-7-0010, DX-7-0012, DX-7-0013 .) In the presentation, Dr. Nørgaard again concluded that "[t]he need for high plasma levels is overestimated," and that "[a]ntidiuresis can be obtained by low plasma levels," such as the plasma levels shown in the 45A07-39 study below 5 pg/mL:



(DX-7-0023.) He also stated that "[i]ncreased exposure extends duration of action." [Anticipated testimony of Dr. Nørgaard]

DFF351. In addition to his internal statements to Ferring management, Dr. Nørgaard also made similar statements to regulatory authorities in early 2000. (*See* DX-29-0001 ("After some discussion, Jens Peter Nørgaard (JPN) gave his presentation on clinical and safety issues. He stated clearly that increased exposure would lead to increased duration of action, and that this could eventually lead to increased water intake in the morning and risk for hyponatremia.").) [Anticipated testimony of Dr. Nørgaard]

f) PK/PD Report—October 2000

DFF352. Dr. Nørgaard's opinions were memorialized in a PK/PD expert report titled "Pharmacokinetics and pharmacodynamics of orally administered desmopressin (dDAVP)"

dated October 10, 2000 and signed by Thomas Senderovitz, having prepared the report, and Dr. Nørgaard, having reviewed it. (DX-8.) The report was drafted to support regulatory applications and summarizes pharmacokinetic data from Ferring's desmopressin clinical studies, including 45A07-39. Dr. Nørgaard and Dr. Senderovitz again concluded in the expert report that:

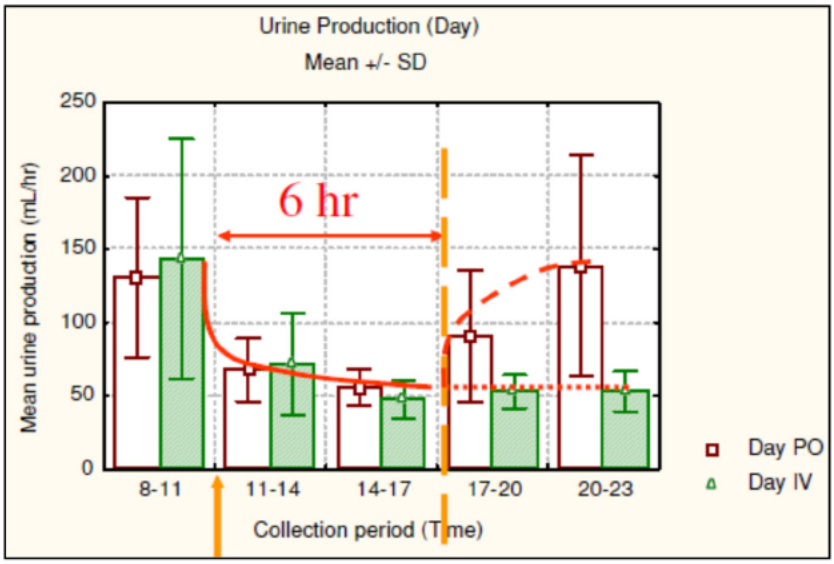
> Increased doses of dDAVP (and hence increased plasma concentrations) result in prolonged duration of pharmacological action — not necessarily more pronounced antidiuretic effects (in terms of urine production or urine osmolality changes).

(DX-8-0003.) [Anticipated testimony of Dr. Nørgaard]

g) Joint Ferring-Aventis Meeting to Discuss the Nocturia Indication for the Oral Tablet—October 2000

DFF353. On October 18, 2000, Ferring met with its U.S. marketing partner, Aventis, regarding the nocturia indication for the oral tablet. (DX-27.) Dr. Nørgaard presented a review of some Phase II desmopressin trials, as indicated in the agenda, and Thomas Senderovitz presented a PK/PD review. (DX-27-0001.) [Anticipated testimony of Dr. Nørgaard]

DFF354. In his presentation slides (DX-9), Dr. Senderovitz summarized the pharmacokinetic results from Ferring's 45A07-39 study, including the plot of desmopressin plasma concentrations showing that 200 µg tablets produced peak plasma concentrations below 10 pg/mL with a duration of effect of about six hours. (DX-9-0014.) Dr. Senderovitz concluded from the 45A07-39 data that desmopressin is "effective even at *very* low plasma concentrations" and that higher plasma levels result in "*longer* antidiuretic effect" (as opposed to greater antidiuretic effect). (DX-9-0020.) Specifically, Dr. Senderovitz noted a six-hour duration of action in the 45A07-39 study:



(DX-9-0018.) Dr. Senderovitz also explained that a modeling study (the EMF study) was being developed to further investigate the relationship between desmopressin pharmacokinetics and clinical effect. (DX-9-0042.) [Anticipated testimony of Dr. Nørgaard]

h) The EMF Study

DFF355. In order to further refine Ferring's understanding of the dose/response relationship of desmopressin, Dr. Senderovitz and Dr. Nørgaard met with scientists from EMF Consulting in October 2000 to initiate a new PK/PD modeling study. (DX-10-0001; DX-11-0001.) [Anticipated testimony of Dr. Nørgaard]

DFF356. The population modeling was designed to "establish a population PK/PD model for desmopressin in nocturia to be used for prediction and simulation . . . ." (DX-11-0001.) Another stated goal of this project, according to the meeting minutes, was "to help the justification of dose selection." (DX-11-0001) The meeting minutes reflect Dr. Nørgaard's goal of identifying a low enough dose of desmopressin to shorten the antidiuretic effect to avoid side effects. The minutes state that "ideally we want to stop the anti-diuretic effect before the patients wake up and start to take fluids." (DX-11-0002.) [Anticipated testimony of Dr. Nørgaard]

DFF357. A key goal of the EMF study was to generate an estimate of the EC_{50} value for desmopressin, which is a value of the plasma concentration at which desmopressin provides half of the maximum antidiuretic effect. [Anticipated testimony of Dr. Nørgaard]

DFF358. On February 19, 2002, EMF Consulting presented on its findings, followed by the publication of a final report in May 2002. (DX-12.) The value of the EC_{50} calculated from the modeling was about 0.7 pg/mL in nocturia patients for both the urine production and duration of first sleep episode endpoints. (DX-12-0061.) That finding was consistent with Dr. Nørgaard's and Dr. Senderovitz's previous understanding that desmopressin is a very potent antidiuretic drug. [Anticipated testimony of Dr. Nørgaard]

DFF359. The following month, in March 2002, Ferring prepared a report to support regulatory activities in Europe, in which Ferring estimated that a 20 µg dose of the orodispersible formulation would result in an expected plasma level of about 1.5 pg/mL, which would still be enough to generate maximal or near-maximal antidiuresis based on the results of the EMF study. (DX-15-0004 to DX-15-0005.) [Anticipated testimony of Dr. Nørgaard]

DFF360. And on March 22, 2002, Dr. Senderovitz explained how the results of the EMF study could be used to justify the selection of doses for Ferring's future clinical studies in a "Summary of the Pharmacokinetics/Pharmacodynamics of desmopressin administered either via the marketed tablet or via the NEWMIN—a new orodispersible formulation." (JX-10.) Specifically, Dr. Senderovitz explained:

> In a recently finalised population PKPD analysis of several clinical Phase I and II studies in adults, the plasma desmopressin-response (urinary output) relationship was estimated for healthy volunteers (hydrated and normally hydrated) as well as patients (nocturia and diabetes insipidus patients) [2]. This analysis of Minirin in adults showed that *the EC_{50} with respect to urinary output is very low* (Figure 2), [2]. *Thus, near-maximal or maximal antidiuresis can be expected even at plasma desmopressin concentrations as low as 1.5-*

> *2 pg/ml,* i.e. below the limit of quantitation of the current used assay (LOQ 2.5 pg/ml). As the geometric mean C_{max} of desmopressin after the administration of a 200 µg NEWMIN was approximately 14 pg/ml, one tenth of such dose would result in a plasma level of around 1.5 pg/ml, i.e. a level that would still induce significant antidiuresis. *This opens up the possibility of studying lower doses of desmopressin than currently marketed.* Thus, in the currently planned study program for nocturia associated with nocturnal polyuria, *the dose-response study will include a low dose (lower than 40-50 µg NEWMIN)*, thus allowing for a complete dose-response relationship for this indication and *a possibility for initiating therapy at lower doses*.

(JX-10-0005 (emphasis added).) [Anticipated testimony of Dr. Nørgaard]

DFF361. Ferring ultimately used the results of the EMF study, specifically the EC_{50} value, to determine the doses for Ferring's orodispersible formulation to test in future clinical studies, including CS009. [Anticipated testimony of Dr. Nørgaard]

2. Post-August 2001 activities

a) CS004

DFF362. In the second half of 2001 and in early 2002, Dr. Senderovitz and his pharmacokinetics department at Ferring designed and conducted a study to determine the absolute bioavailability of Ferring's new orodispersible formulation of desmopressin. The study was designated CS004. (DX-13-0001.) [Anticipated testimony of Dr. Nørgaard]

DFF363. The final clinical trial protocol was drafted as of December 13, 2001. (DX-13-0001.) The study, titled, "Absolute bioavailability of three different doses of desmopressin in an orodispersible tablet in healthy non-smoking male volunteers," was designed to administer the orodispersible formulation in doses of 200, 400, and 800 µg. The clinical team for the study included, among others, Thomas Senderovitz and Kristian Juul, but not Dr. Fein. [Anticipated testimony of Dr. Nørgaard]

DFF364. They reasoned that the chosen doses, particularly 200 µg and 400 µg, were tested and validated in nocturia but, since the 200 µg dose of the oral tablet gave hardly detectable plasma concentrations, the team wanted to ensure that they could actually measure the plasma levels of desmopressin in the study subjects. Therefore, they added the 800 µg dose. [Anticipated testimony of Dr. Nørgaard]

DFF365. The CS004 study was conducted between January 30, 2002 and March 8, 2002. The results of the CS004 study demonstrated that the mean bioavailability of Ferring's orodispersible formulation of desmopressin was determined to be about 0.3%. (JX-10-0002; *see also* DX-19-0045.) [Anticipated testimony of Dr. Nørgaard.]

b) CS007 and CS009

DFF366. By March 2002, Dr. Senderovitz and Dr. Nørgaard were designing clinical studies for the new orodispersible formulation of desmopressin based on both the EC_{50} value of about 0.7 pg/mL from the EMF study and the 0.3% bioavailability of the new orodispersible formulation from the CS004 study. (JX-10-0002, JX-10-0005.) Dr. Senderovitz proposed testing doses that would achieve a C_{max} as low as 1.5 pg/mL with a 20 µg orodispersible tablet. [Anticipated testimony of Dr. Juul, Dr. Nørgaard.]

DFF367. Based on the EC_{50} value of desmopressin and the 0.3% bioavailability, Dr. Senderovitz and his team selected doses for both the CS007 and CS009 clinical studies targeting plasma concentrations equal to the EC_{50} value and multiples thereof. For example, the CS007 study was designed to test the orodispersible formulation in doses of 10, 20, 40, 80, and 160 µg doses of desmopressin, which based on the bioavailability of the orodispersible tablet, corresponds to doses expected to provide multiple of 1, 2, 4, 8, and 16 of the EC_{50} value of desmopressin. (DX-16-0005.) [Anticipated testimony of Dr. Juul, Dr. Nørgaard.]

DFF368. The CS007 clinical study protocol explains the rationale for these low doses, stating that "[i]n the present study doses range from much lower than previously investigated to doses thought to be comparable to the currently recommended [doses]." (DX-16-0024.) This section further states that "[t]he study will improve[] the knowledge about the PK/PD relationship of low doses of [the] new formulation as well as the duration of action of the different doses of desmopressin." (DX-16-0024.) [Anticipated testimony of Dr. Nørgaard.]

DFF369. The CS007 clinical study protocol was therefore designed not only to further verify Dr. Nørgaard's and Dr. Senderovitz's conclusions regarding the efficacy of very low doses of desmopressin, as well as reducing the risk of hyponatremia, but also to gain a more complete understanding of the full dose/response relationship for desmopressin. (DX-16-0023.) [Anticipated testimony of Dr. Nørgaard.]

DFF370. Ferring experienced delays in the production of orodispersible tablets for its clinical trials, including CS007. (DX-17-0004.) Because of these delays, in June 2002, Dr. Senderovitz's pharmacokinetics group prepared a draft protocol for an alternative study in which the desmopressin would be administered intravenously (via "i.v."), designated CS009, using the same rationale for dosing as explained for CS007, but based on i.v. administration. (DX-18-0019.) To approximate the orodispersible doses from CS007, Dr. Senderovitz calculated i.v. doses of 30, 60, 125, 250, and 500 ng. [Anticipated testimony of Dr. Nørgaard.]

DFF371. A preliminary summary report of the results of CS009, dated October 4, 2002, showed that the 0.9 and 1.8 ng/kg doses in CS009 achieved a duration of antidiuretic effect lasting for no more than between about 4 and about 6 hours for the 0.9 and 1.8 ng/kg doses. (DX-23-0003.) [Anticipated testimony of Dr. Juul, Dr. Nørgaard.]

D. There is no contemporaneous written record of any conception by Dr. Fein that corroborates his purported invention

1. Summer 2001

DFF372. Dr. Fein has previously pointed to events in the summer of 2001 for corroboration of his invention, but has admitted there is no written documentation for his discussions with Dr. Nardi or his discussions with the team members for the new orodispersible formulation of desmopressin—the NewMin (or new Minirin) team—in Copenhagen and that the purpose of the Copenhagen meetings was to introduce himself. [Anticipated testimony of Dr. Fein.]

DFF373. He admitted he did not attend any of the meetings in Copenhagen in August 2001 specifically focused on the NewMin project. [Anticipated testimony of Dr. Fein.]

DFF374. The only written documentation of Fein's work on desmopressin while in Copenhagen in August 2001 is a meeting agenda and handwritten time logs that do not confirm meetings were held, the substance of those meetings, or whether only non-desmopressin projects like Degarelix were discussed. [Anticipated testimony of Dr. Fein.]

2. CS004

DFF375. Dr. Fein has claimed that Ferring's clinical trial CS004 was designed and conducted as the first step to testing one element of his inventions, namely that sublingual administration would produce higher bioavailability. [Anticipated testimony of Dr. Fein.]

DFF376. There is no documentary evidence corroborating (i) Dr. Fein's alleged contribution to CS004 or (ii) that CS004 was designed to test his allegedly inventive concept regarding sublingual absorption.

DFF377. Dr. Fein has admitted that he did not provide any specific wording for the CS004 protocol, which was already being prepared in August 2001, (*see* DX-40 (dated August

30, 2001)), when Dr. Fein, for the first time, purportedly disclosed his alleged concepts to Ferring. [Anticipated testimony of Dr. Fein.]

DFF378. At trial in the 2012 action, in response to the question whether Dr. Fein communicated any specific contributions for the CS004 protocol to others, Dr. Fein testified that he had an undated conversation with someone, "most likely" Senderovitz, though Fein "d[id]n't recall specifically." He has no documents to substantiate the substance or date of this conversation. [Anticipated testimony of Dr. Fein.]

DFF379. Moreover, there was a CS004 Clinical Team Meeting (DX-25) on October 29, 2001, for which Dr. Fein was ***not*** (i) listed among the participants; (ii) among the individuals called for the meeting; (iii) "even invited to the meeting;" or (iv) even "aware of the meeting." Moreover, Dr. Fein had not seen the minutes for this meeting until trial in the 2012 action. He even admitted that he attended none of the project team meetings planning CS004. [Anticipated testimony of Dr. Fein.]

DFF380. Dr. Fein has admitted that:

- despite his testimony that CS004 was created to test his ideas, there are no documents illustrating that he had any role in designing or conducting CS004;
- he certainly did not contribute to the clinical study report for CS004; and
- he is not aware of any written record to suggest that CS004 was created to test his ideas or concepts.

[Anticipated testimony of Dr. Fein.]

DFF381. The evidence shows that Dr. Senderovitz—not Dr. Fein—led the design of CS004 from Copenhagen. Dr. Senderovitz's involvement is memorialized in various documents in the fall of 2001, including as the "Director Clinical Pharmacology & Pharmacokinetics" in minutes for the October 29, 2001 CS004 Clinical Team Meeting (DX-25) and the October and

December protocols (DX-26 and DX-13, respectively)—documents that do not mention Dr. Fein at all. [Anticipated testimony of Dr. Nørgaard.]

3. CS009

DFF382. Dr. Fein had alleged that CS009 was designed to test his "low-dose hypothesis." He also alleges that his handwritten notes reflect his comments on the draft CS009 protocol and many of his suggested changes, including his thoughts regarding single-digit picogram-per-milliliter plasma levels being desirable. [Anticipated testimony of Dr. Fein.]

DFF383. But Dr. Fein was provided with a complete draft protocol that included dosing information determined by the EMF study—a study in which he had no involvement. Specifically, on June 7, 2002 (after the May 7, 2002 filing date of GB '397), Dr. Senderovitz's clinical pharmacology group sent Dr. Fein a clinical trial protocol for CS009 dated June 6, 2002. (DX-21.) [Anticipated testimony of Dr. Fein.]

DFF384. When Dr. Fein received the draft CS009 protocol, he had not drafted any portion of it, nor had he discussed the specific design of the study with anyone at Ferring. [Anticipated testimony of Dr. Fein.]

DFF385. Moreover, the draft already contained complete dosing selections based on the EC_{50} of desmopressin from the EMF study and the bioavailability of the orodispersible formulation. (DX-21-0018 to DX-21-0019.) [Anticipated testimony of Dr. Fein.]

DFF386. Dr. Fein has admitted that the doses in CS009 were based on the EC_{50} value calculated in the EMF study. But Dr. Fein had no involvement in the EMF study. [Anticipated testimony of Dr. Fein.]

DFF387. Dr. Fein has also admitted his calculations never changed the specific level of doses but, instead, basically converted their units to weight-based ng/kg. [Anticipated testimony of Dr. Fein]

DFF388. The only change in dosing made by Dr. Fein was to eliminate the top two doses, but Dr. Fein has admitted that going from five doses to three doses does not generate any data that would not have been available from the original five-dose study. [Anticipated testimony of Dr. Fein]

DFF389. The documents related to CS009 show (i) that the doses in the CS009 study came from the EMF study, which was initiated by Dr. Senderovitz and completed before Dr. Fein claims to have become involved with the CS009 study, and (ii) no substantive contribution to the CS009 study by Dr. Fein.

E. Dr. Fein derived the subject matter recited in the claims of the patents in suit from Dr. Nørgaard and Dr. Senderovitz

DFF390. As shown above, the idea of low doses based on potency of desmopressin was known in the prior art and Dr. Nørgaard's articles and presentations prior to August 2001.

DFF391. As shown above, Ferring had already by August 2001 hired EMF Consulting to establish dosing amounts for the orodispersible formulation, and the results of the EMF Consulting tests along with the results of CS004 led to the lower doses in subsequent clinical studies.

DFF392. Example 7 of the common specification is based on Ferring's clinical study designated CS004, to which Dr. Fein had no involvement. [Anticipated testimony of Dr. Fein.]

DFF393. Example 8, which was added to the common specification in Dr. Fein's PCT '463, is essentially a copy of the protocol Ferring's CS009 study. [Anticipated testimony of Dr. Fein.]

DFF394. Dr. Fein has claimed that CS009 was designed to test his "low-dose hypothesis," but the doses in the CS009 study came from the EMF study, which was initiated by Dr. Nørgaard and Dr. Senderovitz and was completed before Dr. Fein claims to have become involved with the CS009 study. [Anticipated testimony of Dr. Fein.]

DFF395. Dr. Fein was provided with a complete draft protocol of CS009 on June 7, 2002 that contained complete dosing selections based on the EC_{50} of desmopressin from the EMF study and the bioavailability of the orodispersible formulation. [Anticipated testimony of Dr. Fein.]

DFF396. Dr. Fein signed the final version of the CS009 protocol on August 21, 2002 as the study sponsor. (DX-20-0010.) The first page of the protocol notes, "The confidential information in this document in the property of FERRING. It is understood that this information will not be disclosed to any third party, in any form, without prior written authorization from FERRING Research and Development, US." (DX-20-0004.) [Anticipated testimony of Dr. Fein.]

DFF397. The CS009 study was completed in September 2002. CS009 confirmed the measurable effect of desmopressin at low doses when administered intravenously. (DX28.) Dr. Fein traveled to Copenhagen in Fall 2002 to present the results to the head of Ferring's clinical research department. [Anticipated testimony of Dr. Fein, Dr. Nørgaard.]

DFF398. Dr. Fein was terminated in November 2002. [Anticipated testimony of Dr. Fein.]

DFF399. Before Dr. Fein was terminated, he had access to Dr. Nørgaard and Dr. Senderovitz's work on desmopressin done at Ferring. [Anticipated testimony of Dr. Fein.]

DFF400. On October 21, 2002, prior to leaving his position at Ferring, Fein established his own consultancy, "CNF Pharma." "CNF" stood for Cheng, Nardi, and Fein and was created while Maria Cheng, Dr. Nardi, and Dr. Fein continued to work for Ferring. Dr. Cheng and Dr. Fein were consultants, but Nardi was a senior employee who owed a fiduciary duty to Ferring. [Anticipated testimony of Dr. Fein.]

[redacted]

DFF406. Dr. Fein's Example 8 is essentially a copy of Ferring's CS009 study, which was based on Dr. Senderovitz's and Dr. Nørgaard's dose selection and targeted plasma concentrations predicated on the 0.7 pg/mL EC_{50} value and the 0.3% bioavailability of Ferring's orodispersible formulation. (DX-20-0016 to DX-20-0017; DX-22-0012 to DX-22-0013.) [Anticipated testimony of Mr. Vis.]

VI. The Patents in Suit Are Unenforceable Due to Inequitable Conduct

DFF408. Ferring filed the GB application on May 7, 2002, which was directed to an orodispersible formulation of desmopressin. The GB application did not name any inventors. (JX-3-0001.) (DFF2; DFF49; DFF330.)

DFF409. Dr. Fein was admittedly not involved in the development of the orodispersible formulation of desmopressin. [Anticipated testimony of Dr. Fein]

DFF410. The GB application included eleven examples, Example 1-7 and Comparative Examples 1-4. (DFF62.)

DFF411. Dr. Fein was not involved in Examples 1-7 or Comparative Examples 1-4.

DFF412. Example 7 of the common specification is based on Ferring's clinical study designated CS004, to which Dr. Fein had no involvement. (DFF66; DFF375-DFF381.)

DFF413. PCT '463 was filed by Dr. Fein, through his counsel, on May 6, 2003 and included a claim for priority to the GB application. (DFF2.)

DFF414. The '100 application was filed by Dr. Fein, through his counsel, on November 12, 2003, as a continuation-in-part of PCT '463. (DFF2.)

DFF415. Dr. Fein added certain new disclosures to the '100 application that were not present in his earlier PCT '463 application, including Example 8 and Figures 1-9. (DFF51; DFF332.)

A. Dr. Fein copied Ferring's CS009 and represented it as his own work by including it as Example 8

DFF416. Dr. Fein has alleged that CS009 was designed to test his "low-dose hypothesis" but the doses in the CS009 study and its overall design came from Dr. Senderovitz and the doses were based on the EC_{50} generated from the EMF study and the bioavailability from the CS004 Ferring study. (DFF382-DFF389; DFF394.)

DFF417. The CS009 study was completed in September 2002. Dr. Fein traveled to Copenhagen in Fall 2002 to present the results to the head of Ferring's clinical research department. (DFF37.)

DFF418. Dr. Fein was terminated in November 2002. (DFF398.)

DFF419. On October 21, 2002, prior to leaving his position at Ferring, Dr. Fein established his own company called "CNF Pharma." "CNF" stood for Cheng, Nardi, and Fein and was created while Maria Cheng, Dr. Ron Nardi, and Dr. Fein continued to work for Ferring. Maria Cheng and Dr. Fein were consultants, but Dr. Nardi was a senior employee who owed a fiduciary duty to Ferring. [Anticipated testimony of Dr. Fein.]

[redacted]

B. Reliance on Example 8 for patentability

DFF423. Dr. Fein repeatedly argued to the PTO that Example 8 supported the patentability of then-pending claims during prosecution of the patents in suit.

1. Prosecution of the '100 application

DFF424. During prosecution of the '100 application, applicants (i.e., Dr. Fein) submitted new claims in a preliminary amendment and argued that support for those claims could be found, *inter alia*, in Example 8. Specifically, applicants referred the Examiner to

Example 8 to support language added to the claims (directed to the purported discovery of "low doses [being] sufficient to decrease urine production yet minimize or eliminate the induction of hyponatrmia [sic]"). (JX-9-0151.) Applicants also referred the Examiner to Example 8 for the disclosure of "administration to achieve a desmopressin blood concentration within the range claimed and show[ing] specifically the antidiuretic effect" (JX-9-0499; *see also* JX-9-1222). [Anticipated testimony of Fein.]

2. Prosecution of the '203 patent and reexamination

DFF425. During prosecution of the '203 patent, applicants (i.e., Dr. Fein) again submitted new claims in a preliminary amendment. (JX-7-0064.) The three new independent claims contained the following limitations:

- "to maintain a desmopressin plasma/serum concentration within the range of about 0.5 pg/ml and 10 pg/ml for at least four to six hours" (then pending claim 19);
- "in an amount and for a time sufficient to establish a serum/plasma desmopressin concentration no greater than about 10 pg/ml" (then pending claim 29); and
- "in an amount and for a time sufficient to establish a serum/plasma desmopressin concentration greater than 0.1 pg/ml plasma/serum and less than about 10 pg/ml plasma/serum for a time greater than four hours" (then pending claim 33).

(JX-7-0013 to JX-7-0014.)

DFF426. Applicants (i.e., Dr. Fein) argued that support for those new claims could be found in, *inter alia*, Example 8. (JX-7-0064 (referring the Examiner to "page 36, first paragraph; Tables 1-6 and Figures 1-9; and page 31, top paragraph" of the Preliminary Amendment, all of which are portions of Example 8, as "[s]upport for new claims 19-34" (*see* JX-7-0056, JX-7-0053 to JX-7-0055, JX-7-0004 to JX-7-0012, JX-7-0051.)

DFF427. Later during prosecution of the ’203 patent, applicants (i.e., Dr. Fein) submitted a Declaration of Thomas Berl, MD (“the Berl Declaration”) (JX-7-0229 to JX-7-0256) in response to an Office Action rejecting the then pending claims for, *inter alia*, anticipation. In the Berl Declaration, Dr. Berl relied on Example 8 in arguing why the claims were not anticipated by the cited prior art. (JX-7-0231 to JX-7-0232.)

DFF428. In the Notice of Allowance, the Examiner relied on the Berl Declaration, stating “the affidavit is sufficient to overcome the rejections of record under 35 USC 102.” (JX-7-0312.)

DFF429. During reexamination of the ’203 patent, the patentee (i.e., Dr. Fein) stated that “[f]rom these studies [Example 8], it was established that the threshold desmopressin blood concentration sufficient to produce an anti-diuresis effect was much lower than the concentrations typically achieved in prior art practice.” (DX-35-0003.)

3. Prosecution of the ’321 patent

DFF430. During prosecution of the ’321 patent, applicants (i.e.., Dr. Fein) submitted new claims in a preliminary amendment claiming “an antidiuretic effect” (then pending claims 19, 20, 21) and stated that support of the claimed subject matter can be found “in Example 8 (see paragraph bridging pages 30-31 for subject matter of *antidiuretic effect*.”) (JX-8-0081 and JX-8-0084 (emphasis in original).)

DFF431. In the same submission, applicants added claims claiming a method to “produce an antidiuretic effect lasting for a maximum of between about 4 and about 6 hours” (then pending claims 20 and 21) and stated that support of the claimed subject matter can be found “in the paragraph bridging pages 31-32 and the first paragraph on page 36 and the

drawings [i.e., Example 8] (regarding the subject matter of *maximum duration*)" (JX-8-0081 and JX-8-0084 (emphasis in original).)

DFF432. In the same submission, applicants added a claim claiming "a method for inducing voiding postponement comprising administering to a patient an amount of desmopressin sufficient to produce in the patient a urine osmolality ranging above about 300 mOsm/kg for less than about 5 hours after administration" (then pending claim 27) and referred the Examiner to "Figs. 8 and 9 [added as part of Example 8] (where osmolality of urine is shown to increase to above about 300 mOsm/kg for just under 5 hours in a preferred dose)". (JX-8-0082 and JX-8-0084.) [Anticipated testimony of Fein.]

DFF433. The PTO issued an Office Action dated January 12, 2009 rejecting the pending claims for, *inter alia*, anticipation and obviousness. (JX-8-0152.)

DFF434. In response to the January 12, 2009 Office Action, applicants cancelled some claims, amended others, and added new claims claiming, *inter alia*, "no more than about 2/ng/kg" (then pending claim 20) and "no more than about 1 ng/kg" (then pending claim 21). (JX-8-0173 to JX-8-0175.) Applicants stated that "[b]ases for the 2 ng/kg and 1 ng/kg limitations are present in the examples showing the effects of delivering these quantities of desmopressin to the bloodstream of the test patients: see the tables on page 33, 34, and 35 and the drawings." (JX-8-0176.) Pages 33, 34, 35 and the drawings refer to the tables and drawing in support of Example 8. (*See* JX-8-0041 to JX-8-0043, JX-8-0050 to JX-8-0058.)

DFF435. In that same response to the January 12, 2009 Office Action, applicants argued, *inter alia*, that the prior art cited by the Examiner did not anticipate then pending claim 20 and dependent claims 21-26 and 28-33 based on the "2 ng/kg" limitation and the "lasting between about 4 and about 6 hours" limitation. (JX-8-0178.) Applicants also argued that the

prior art did not anticipate then pending claims 27 based on the "for less than about 5 hours after administration" limitation. (JX-8-0180; *see also* JX-8-0181 (arguing prior art did not anticipate then pending claim 38 and dependent claim 40 based on the "maximum of about four to about six hours" limitation); JX-8-0181 (arguing prior art did not anticipate then pending claim 39 and dependent claim 40 based on the "no more than about 2 ng/kg" limitation).

DFF436. The Examiner then issued the Notice of Allowance and stated that "[w]hile the prior art teaches desmopressin compositions and the use for voiding postponement, the art previously recognized the necessary dose to be significantly higher than that which is instantly administered, such that administering a 'low' dose as claimed is unobvious and presents an unexpected result." (JX-8-0487 to JX-8-0488.)

C. Dr. Fein submitted a false declaration swearing he was the sole inventor of the patents in suit

DFF437. Dr. Fein filed inventor declarations under penalty of perjury during prosecution of the '100 application (JX-9-0061 to JX-9-0062), the '203 patent (JX-7-0143 to JX-7-0144), and the '321 patent (JX-8-0074 to JX-8-0075) (collectively, "Combined Declaration"). [Anticipated testimony of Fein.]

DFF438. Dr. Fein's Combined Declaration acknowledged that he was subject to the duties under 37 C.F.R. 1.56 and declared that

> "all statements made [in the Combined Declaration] of [his] own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under [18 U.S.C. § 1001] **and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom**."

(JX-9-0061 to JX-9-0062 (emphasis added); JX-7-0143 to JX-7-0144 (emphasis added); JX-8-0074 to JX-8-0075 (emphasis added).) [Anticipated testimony of Fein.]

DFF439. Dr. Fein's Combined Declaration swears that he is the sole inventor of the subject matter claimed in the patents in suit. (JX-9-0061 to JX-9-0062; JX-7-0143 to JX-7-0144; JX-8-0074 to JX-8-0075.) [Anticipated testimony of Fein.]

DFF440. Dr. Fein knew that Example 8 was derived from Ferring's work.

DFF441. Dr. Fein's reliance on Example 8 for patentability render his claims of sole inventorship unmistakably false.

DFF442. Dr. Fein's submission of a false declaration was an egregious affirmative act.

DFF443. The most reasonable inference from Dr. Fein's submission of a false declaration claiming sole inventorship—knowing that he did not invent the subject matter relying upon Example 8—is that Dr. Fein submitted his false declaration with the intent to deceive the PTO.

VII. Counterclaimants Have Not Shown That Ferring Directly Infringes the Asserted Method Claims Under 35 U.S.C. § 271(a)

DFF444. Ferring engages in pharmaceutical research and development activities, but Ferring, like most pharmaceutical companies, generally does not treat diseases.

DFF445. Counterclaimants have put forth no evidence that Ferring itself has practiced the claimed methods of use with NOCDURNA.

DFF446. Counterclaimants have put forth no evidence that Ferring employs or otherwise has an agency relationship with any individual who has practiced the claimed methods of use with NOCDURNA.

VIII. Counterclaimants Have Not Shown That Ferring Indirectly Infringes the Asserted Claims Under 35 U.S.C. § 271(b) or 35 U.S.C. § 271(c)

A. Counterclaimants have not shown that there is a direct infringer

1. Counterclaimants have not shown a single instance of actual direct infringement

DFF447. On June 21, 2018, the FDA approved Ferring's NDA No. 022517 which granted Ferring approval to sell its NOCDURNA drug product in the United States. (PX-13 at FERSER0367487.)

DFF448. After the FDA approved NOCDURNA, Counterclaimants filed a motion for a preliminary injunction seeking to block Ferring from selling NOCDURNA in the United States. (D.I. 117.) On November 8, 2018, the Court issued a memorandum opinion and order denying Counterclaimants' request for a preliminary injunction. (D.I. 300.) The following day—November 9, 2018—Ferring launched NOCDURNA in the United States. Ferring has sold NOCDURNA continuously since that time. [Anticipated testimony of Mr. Carter.]

[redacted]

DFF450. Despite these sales, Counterclaimants have not shown a single instance of NOCDURNA being used to treat a patient by administering a dose of NOCDURNA to achieve the desmopressin plasma concentrations claimed in the asserted claims of the ’203 patent or claims 6 and 7 of the ’321 patent.

DFF451. Despite these sales, Counterclaimants have not shown a single instance of NOCDURNA being used to treat a patient by administering a dose of NOCDURNA to deliver less than about 2 ng/kg to the patient’s bloodstream and to reduce the risk that a patient develops hyponatremia, as required by the asserted claims of the ’321 patent.

DFF452. Despite these sales, Counterclaimants have not shown a single instance of NOCDURNA being used to treat a patient by administering a dose of NOCDURNA that is therapeutically effective to produce an antidiuretic effect lasting for no more than between about 4 and about 6 hours and to reduce the risk that a patient develops hyponatremia, as required by the asserted claims of the ’321 patent.

DFF453. Despite these sales, Counterclaimants have not shown a single instance of NOCDURNA being used to treat a patient by administering a dose of NOCDURNA to raise the patient’s urine osmolality above about 300 mOsm/kg for less than about 5 hours after administration and to reduce the risk that a patient develops hyponatremia, as required by asserted claim 12 of the ’321 patent.

2. Counterclaimants have not shown that administration of NOCDURNA to a patient will necessarily result in infringement of the asserted claims

a) Counterclaimants' reliance on Ferring's clinical studies does not show that administration of NOCDURNA to patients will necessarily result in infringement of the asserted claims

DFF454. Counterclaimants' infringement analysis relies on mean pharmacokinetic and pharmacodynamic data, rather than individual data, from certain of Ferring's clinical studies, specifically CS006, CS007A, CS021, and CS030.

DFF455. As an initial matter, as discussed above, the pharmacokinetics and pharmacodynamics of desmopressin formulations typically exhibit a high degree of variability. Because of this variability, a mean value is not representative of any specific individual within the population. [Anticipated testimony of Dr. Juul, Dr. Spaans.]

DFF456. Further, none of the clinical studies on which Counterclaimants rely are in patients suffering from nocturia due to nocturnal polyuria. [Anticipated testimony of Dr. Juul, Dr. Spaans.]

b) Administration of NOCDURNA to patients does not necessarily result in plasma concentrations within the claimed plasma concentration ranges

DFF457. The use of NOCDURNA will not necessarily result in desmopressin plasma concentrations within the claimed plasma concentration ranges, which is a necessary predicate to finding indirect infringement where, as here, Counterclaimants have not shown that actual infringement has occurred. [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

(1) The asserted claims with plasma concentration limitations

DFF458. Asserted claim 6 of the '203 patent requires "a maximum desmopressin plasma/serum concentration no greater than 10 pg/ml." (JX-1-0026 at cl. 1, 6.) However,

asserted claim 6 of the '203 patent also requires that the desmopressin plasma concentrations be "maintain[ed] the concentration within the range of about 0.5 pg/ml and 10 pg/ml for about four to six hours." (JX-1-0026 at cl. 1, 6.)

DFF459. Asserted claims 10 and 11 of the '203 patent require "establish[ing] a maximum serum/plasma desmopressin concentration no greater than 10 pg/ml." (JX-1-0026 at cl. 10, 11.)

DFF460. Asserted claim 12 of the '203 patent requires "establish[ing] a serum/plasma desmopressin concentration no greater than about 5 pg/ml." (JX-1-0026 at cl. 12.)

DFF461. Asserted claim 13 of the '203 patent requires "establish[ing] a maximum serum/plasma desmopressin concentration greater than 0.1 pg/ml and less than 10 pg/ml." (JX-1-0026 at cl. 13.)

DFF462. Asserted claim 6 of the '321 patent requires "produc[ing] a plasma/serum desmopressin concentration in the patient of a maximum of no more than about 10 pg/ml." (JX-2-0027 at cl. 6.)

DFF463. Asserted claim 7 of the '321 patent requires "produc[ing] a plasma/serum desmopressin concentration in the patient of a maximum of no more than about 5 pg/ml." (JX-2-0027 at cl. 7.)

(2) Dose linearity

DFF464. Ferring's NDA documents state that "[d]esmopressin shows dose linearity regarding AUC and C_{max} in the range of 60 to 240 mcg. However, the bioavailability of doses below 60 has not been evaluated." (PX-6 at FERSER0000230.) In other words, the bioavailability of the 25 µg and 50 µg doses has not been evaluated and the dose linearity for

doses of Ferring's orodispersible tablet formulation below 60 µg has not been confirmed. [Anticipated testimony of Dr. Spaans.]

DFF465. Counterclaimants rely on the clinical study report for Ferring's CS021 study in support of their arguments. (JX-12.) The CS021 study investigated the effects of administering 60, 120, and 240 µg doses of the orodispersible tablet. (JX-12.) Further, as noted above, the CS021 study specifically limited its dose linearity to those doses studied and specifically pointed out that doses below 60 µg had not been evaluated. (PX-6 at FERSER0000230.)

DFF466. These results provide some scientific certainty regarding the interpolation of data concerning doses within that range (i.e., 60 – 240 µg desmopressin), but a POSITA would recognize that even formulations that exhibit relatively stable linear relationships between dose and concentration at certain dose ranges do not show linearity across all possible doses. Specifically, at some point for both the low and high end of the doses, linearity will break down and until studies are conducted to establish those parameters, it is not reasonable to extrapolate data with any scientific certainty based on a supposedly "linear" relationship for those doses tested. [Anticipated testimony of Dr. Spaans.]

DFF467. Further, Counterclaimants rely on Ferring's Biowaiver Request, which was submitted to the FDA to request a waiver from being required to conduct new pharmacokinetic studies with respect to NOCDURNA. According to Counterclaimants' expert Dr. Mayersohn, Ferring "submitted that data to, *inter alia*, support its contention that 'Desmopressin pharmacokinetics is linear over the proposed dose range.'" [Anticipated testimony of Dr. Mayersohn.]

DFF468. However, Counterclaimants do not address Ferring's statements to the FDA in the Biowaiver Request. For example, Ferring stated that "[t]he pharmacokinetic profile cannot be determined to show that desmopressin melt pharmacokinetics is linear over the dose range of 10, 25, 50, and 100 mcg used in the Phase 3 clinical studies, due to the sensitivity limitations of available validated assays." (PX-22 at FERSER0000014.) Ferring also states that the lower doses would "provide insufficient pharmacokinetics (PK) data," (PX-22 at FERSER0000015), and that such data "would provide highly variable and inadequate PK information" (PX-22 at FERSER0000017).

DFF469. The statements in Ferring's biowaiver do not establish that the pharmacokinetics of desmopressin are linear for the 25 µg and 50 µg doses of desmopressin contained in NOCDURNA. Instead, Ferring sought the biowaiver to excuse the lack of pharmacokinetic data because of limitations in testing methodology that prevented Ferring from determining the concentrations resulting from administration of 25 and 50 µg orodispersible doses. [Anticipated testimony of Dr. Spaans, Dr. Juul.]

(3) The plasma concentration data on which Counterclaimants rely is too variable to show that any individual patient necessarily infringes the asserted claims of the '203 patent and asserted claims 6 and 7 of the '321 patent

DFF470. Counterclaimants rely on the summary data from table 9-2 of the CS021 study to extrapolate proposed mean C_{max} values for a patient population alleging that "a 50 mcg dose of desmopressin would yield a mean plasma Cmax of 3.96 pg/ml (20.83% of 19.04 pg/ml, the mean Cmax noted for the 240 mcg dose, for example), and a 25 mcg dose would yield a mean plasma Cmax of 1.98 pg/ml (10.41% of 19.04 pg/ml, the Cmax noted for the 240 mcg dose, for example)." [Anticipated testimony of Dr. Mayersohn.]

DFF471. Counterclaimants' calculations ignore the significant variability in the individual data. Table 9-2 indicates that the standard deviation for the 240 µg C_{max} data is 15.003 pg/ml, or a CV of 83.6%. (JX-12-0065.) On the one hand, Counterclaimants' note that the CS021 study states that: "[t]he inter-subject variability of the desmopressin plasma concentration data, however, was considerably high, which is known from the large variability in absolute oral bioavailability of desmopressin." (JX-12-0068.) On the other hand, Counterclaimants' do not account for this variability in performing their calculations. Instead, Counterclaimants simply assert that linear scaling to adjust for the difference in dose is sufficient to show that NOCDURNA, when administered, will necessarily meet the plasma concentration limitations. Counterclaimants fail to take into account the significant variability in the data. [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

DFF472. Counterclaimants' expert Dr. Mayersohn also purportedly references the Australian and Canadian monographs for the 60, 120, and 240 µg orodispersible tablets. As an initial matter, Counterclaimants have put forward no evidence regarding the Australian monograph. With respect to the Canadian monograph, again, the CV is 59.5% so the data are highly variable. (PX-29 at ASR-FER000000089.) [Anticipated testimony of Dr. Mayersohn.]

DFF473. Counterclaimants also rely on two Ferring patents, United States Patent Numbers 7,560,429 and 7,947,654 ("the Ferring patents"). (PX-24, PX-25.) As an initial matter, the Ferring patents claim priority to the same GB application as the patents in suit. (*Compare* PX-24 at ASR-FER000000153 and PX-25 at ASR-FER000000175-76 *with* JX-1-0001 and JX-2-0001.) Example 7, on which Counterclaimants rely, is identical to Example 7 in the patents in suit. (*Compare* PX-24 at ASR-FER000000162-63 (Example 7) and PX-25 at ASR-FER000000175-76 (Example 7) *with* JX-1-0022 at Example 7 and JX-2-0023 at Example 7.)

Further, the orodispersible tablets in Example 7 are quantitatively different than the NOCDURNA tablets, which may lead to different pharmacokinetic parameters. (*Compare* PX-24 at ASR-FER000000162 (Examples 4, 5, 6) and PX-25 at ASR-FER000000175 (Examples 4, 5, 6) *with* PX-22 at FERSER0000016 (Table 3).) [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

(4) The data relied on by Counterclaimants is in healthy subjects, not patients

DFF474. Finally, with respect to Counterclaimants' alleged evidence of infringement, it is not clear that the pharmacokinetic data on which Counterclaimants rely is for the relevant patient population—i.e., adults with nocturia. For example, CS021 was a study in 24 healthy subjects. (JX-12-0002.) Similarly, the data in Example 7 of the Ferring patents was in "twenty-four healthy non-smoking male volunteers" (i.e., healthy subjects), (PX-25 at 16:39-40), and CS007A and CS030 were also in healthy volunteers. (JX-13-0023; DX-78-0018.) CS006 was in children.

DFF475. Further, the data relied on by counterclaimants all come from controlled clinical studies, which are carefully designed to minimize the introduction of noise through unwanted factors affecting desmopressin pharmacokinetics and pharmacodynamics. These studies do not reflect the real world treatment of patients and Counterclaimants do not account for the fact that a POSITA would expect even more variation in the pharmacokinetic response in the real world, as opposed to a controlled clinical setting. Each patient treated differs in body weight, genetic make-up, food intake, and other parameters which will alter that patient's pharmacokinetic response. Counterclaimants do not explain how, or if it is even possible, to reliably compensate for these factors. [Anticipated testimony of Dr. Spaans.]

c) Administration of NOCDURNA to a patient does not necessarily result in the claimed durations of action

DFF476. Counterclaimants rely on three Ferring studies—CS006, CS007A, and CS030—to allege that administration of NOCDURNA to a patient will necessarily result in the claimed durations of action. Counterclaimants also rely on CS021 and a paper by Yamaguchi et al. ("Yamaguchi 2012") to show that the claimed durations of action are met. [Anticipated testimony of Dr. Mayersohn.]

DFF477. The claim limitation "lasting for no more than between about 4 and about 6 hours" requires that the antidiuretic effect last for a time period close to about 4 hours to about 6 hours. (JX-2-0027 at cl. 1.) [Anticipated testimony of Mr. Vis, Dr. Mayersohn.]

DFF478. The claim limitation "for less than about 5 hours after administration" in claim 8 requires that the antidiuretic effect last for a time period close to about five hours, counting from the time desmopressin is administered, where the indication of antidiuretic effect is a urine osmolality above 300 mOsmol/kg. (JX-2-0027 at cl. 8.) [Anticipated testimony of Mr. Vis, Dr. Mayersohn.]

DFF479. The claim limitation "within the range of about 0.5 pg/ml and 10 pg/ml for about four to six hours" is to achieve a duration of action of approximately four to six hours. [Anticipated testimony of Dr. Mayersohn.]

(1) CS021 does not show that a patient will necessarily achieve the claimed durations of action in asserted claim 6 of the '203 patent or the asserted claims of the '321 patent

DFF480. With respect to the CS021 study, as discussed above, the mean data are insufficient to show that any particular individual will meet the plasma concentration limitations. For the same reasons above, the mean data are insufficient to show that any particular individual

will maintain plasma concentrations within the claimed range for "about four hours to about six hours." (DFF109-DFF112; DFF470-DFF471.)

DFF481. Further, the half-life of desmopressin, which is a function of the clearance of desmopressin from the body, is known to be different in certain individuals, including those with renal impairment. A longer half life indicates that desmopressin is more slowly eliminated from the body, such that plasma concentrations will remain elevated for longer periods, and may also reach higher levels, in these individuals than in healthy subjects. [Anticipated testimony of Dr. Mayersohn.]

(2) CS006 does not show that a patient will necessarily achieve the claimed durations of action in asserted claim 6 of the '203 patent or the asserted claims of the '321 patent

DFF482. With respect to Ferring's CS006 study, that study looked at duration of action in children based on three urine osmolality thresholds (125, 200, and 400 mOsm/kg). (PX-17 at FERSER0001069.) CS006 was designed to evaluate the effect of different dosages of an orodispersible tablet formulation of desmopressin on children suffering from PNE. (PX-17 at FERSER0001069.) NOCDURNA, however, is indicated for adults (i.e., not children) with nocturia (i.e., not PNE).

DFF483. CS006 explicitly recognizes that children and adults will respond to desmopressin differently with respect to pharmacodynamics and indicates that the 30 µg dose "is probably too small a dose for clinical relevance" in adults. (DX-77-0102.) CS006 is not evidence that patients will meet the required durations of action.

DFF484. Further, Counterclaimants appear to rely on the 400 mOsm/kg threshold and the 30 and 60 µg orodispersible tablet formulations to allegedly show that the limitation of

asserted claim 12 of the '321 patent (as it depends from unasserted claim 8) are met. [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

DFF485. The CVs for these durations of action were 150% for the 30 µg dose, and 65% for the 60 µg dose. (PX-17 at FERSER0001070.) [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

DFF486. The median value was 0.5 hours for the 30 µg dose and 3.1 hours for the 60 µg dose. (PX-17 at FERSER001070.) By definition, half of the numbers fall below the median value. Values so far away from five hours cannot infringe the claims. [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

DFF487. Further, the claim limitation in asserted claim 12 of the '321 patent requires "a urine osmolality ranging above about 300 mOsm/kg for less than about 5 hours *after administration*." (JX-2-0027 at cl. 8 (emphasis added).) The duration of action data in CS006 were calculated as "the period the patient has an osmolality above the cut-off level" (DX-77-0051), which is not the same as the "after administration" limitation in asserted claim 12 of the '321 patent (JX-2-0027 at cl. 8).

DFF488. Finally, even assuming that the data in CS006 were relevant to the question of whether the use of NOCDURNA will meet the duration of action limitations, the data are still mean data and, as explained above, mean data for desmopressin are highly variable and thus have little predictive value for any individual patient. Here, the variability indicates that a significant number of individuals will have durations of action significantly longer than the claimed durations. [Anticipated testimony of Dr. Spaans.]

DFF489. The duration of action data in CS006, which is for children with PNE, cannot be used to determine the durations of action in adults with nocturia and the data are

insufficient to extrapolate with confidence the resulting duration of action when considering the use of NOCDURNA in adults with nocturia. [Anticipated testimony of Dr. Spaans.]

(3) Yamaguchi 2012 does not show that a patient will necessarily achieve the claimed durations of action in asserted claim 6 of the '203 patent or the asserted claims of the '321 patent

DFF490. Counterclaimants also rely on a statement in Yamaguchi 2012. Specifically, Counterclaimants allege that Yamaguchi 2012 discloses: "Overall, the duration of antidiuretic action (DOA; time with urine osmolality >200 mOsm/kg) for the 25, 50, and 100 µg doses are 2 h (P = 0.010), 3.45 h (P < 0.001), and 5.74 h (P < 0.001), respectively . . . ." (PX-28 at ASR-FER000000177.) The relevant time periods are 2 hours for the 25 µg dose and 3.45 hours for the 50 µg dose.

DFF491. Yamaguchi 2012 does not report the plasma concentrations associated with the antidiuretic duration of action and so cannot inform the duration of action of asserted claim 6 of the '203 patent. The claimed plasma concentration range is large, with the highest dose being twenty times larger than the lowest dose, so that one would understand that one cannot necessarily translate the plasma concentration to a duration of action and vice versa. Even assuming that a duration of antidiuretic effect necessarily translates to desmopressin plasma concentrations within the claimed range, the durations of action are shorter than that required by the claim limitation. With respect to the asserted claims of the '321 patent, neither of the relevant durations are between about four and about six hours, and it is undisputed that two hours is an insufficient amount of time to meet the duration of action limitations of the asserted claims of the '321 patent. [Anticipated testimony of Dr. Spaans.]

DFF492. The data in Yamaguchi 2012 are mean data, which is highly variable for desmopressin and thus has little predictive value for any individual patient. [Anticipated testimony of Dr. Spaans.]

(4) CS007A does not show that a patient will necessarily achieve the claimed durations of action in asserted claim 6 of the '203 patent or the asserted claims of the '321 patent

DFF493. CS007A[4] was a Ferring study designed to investigate the antidiuretic effect and pharmacokinetics of three dosage strengths of desmopressin (10, 20, and 40 µg) in healthy overhydrated non-smoking adults. (PX-17 at FERSER0001064.) The duration of action (i.e., the time from onset to end of action) was estimated for each subject using three different urine osmolality thresholds—125 mOsm/kg, 200 mOsm/kg, and 400 mOsm/kg. (PX-17 at FERSER0001065.) There were twelve healthy volunteers in the study. (PX-17 at FERSER0001064.)

DFF494. Ferring's Summary of Clinical Pharmacology Studies indicates that "[s]ustained statistically significant mean increases (from 20 to 280 minutes post dose) were observed for the 40 µg dose only." (PX-17 at FERSER0001066.) Further, the Summary of Clinical Pharmacology Studies states that: "few subjects had observations above 200 mOsm/kg and 400 mOsm/kg thresholds for the two higher doses [i.e. 20 and 40 µg]." (PX-17 at FERSER0001066.) [Anticipated testimony of Dr. Mayersohn, Dr. Spaans.]

DFF495. Counterclaimants point to Table 8 from CS007A, reproduced in the Summary of Clinical Pharmacology, which shows the duration of action (in minutes) for the different dosage strengths and urine osmolality thresholds. These data are reproduced below:

[4] Although Counterclaimants make reference to the CS007 study, the data they and their expert Dr. Mayersohn rely on are from the CS007A study.

Dose (µg)	Urine osmolality threshold (mOsm/kg)		
	125	200	400
10	100.0 ± 84.9	60.0 ± 28.3	-
	(n=2)	(n=2)	-
20	117.8 ± 103.7	132.0 ± 94.4	170.0 ± 99.0
	(n=9)	(n=5)	(n=2)
40	127.3 ± 102.9	117.5 ± 95.3	126.7 ± 89.1
	(n=11)	(n=8)	(n=6)

(PX-17 at FERSER0001067.) In the chart above, the n value represents the number of subjects "with an onset of action time and an end of action time that met the defined threshold cut off." (DX-32-0041.) There were twelve subjects in the study, so any value less than n = 12 means that certain individuals did not reach the threshold. The "n" values show that, even at the highest dose of desmopressin, at least one individual had no duration of action even at the lowest urine osmolality, and half of the individuals had no duration of action at the highest threshold. [Anticipated testimony of Dr. Spaans.]

DFF496. Finally, the data in CS007A are mean data, which is highly variable for desmopressin and thus has little predictive value for any individual patient. [Anticipated testimony of Dr. Spaans.]

(5) CS030 does not show that a patient will necessarily achieve the claimed durations of action in asserted claim 6 of the '203 patent or the asserted claims of the '321 patent

DFF497. Ferring's CS030 study was conducted in healthy male and female volunteers and, as relevant to Counterclaimants' assertions, involved administration of a 60 µg dose of desmopressin as an orodispersible tablet. (DX-78-0001.) Rather than rely on the actual data, Counterclaimants rely on a single statement from Ferring's Summary of Clinical Pharmacology Studies. (PX-18 at FERSER0251785.) As with the other studies relied upon by

Counterclaimants, the variability in the pharmacodynamic response is high. Given the variability of the data, the predictive value of the reported mean data for any individual subject is limited. [Anticipated testimony of Dr. Spaans, Dr. Juul, Dr. Mayersohn.]

d) Administration of NOCDURNA to a patient does not necessarily result in delivering less than about 2 ng/kg desmopressin to the bloodstream as required by the asserted claims of the '321 patent

DFF498. The Court stated that the term "delivering to the bloodstream of the patient an amount of desmopressin no more than about 2 ng/kg . . . said amount being therapeutically effective to produce an antidiuretic effect," appearing in claim 1 of the '321 patent, requires no construction except that the claim term "about 2 ng/kg" is construed as "about 2 ng/kg based on the standard 70 kg human body weight estimate." (D.I. 421 at 38.)

DFF499. Counterclaimants argue that administration of NOCDURNA will necessarily infringe the asserted claims of the '321 patent based on the dose and bioavailability of the NOCDURNA formulation, assuming an average weight of 70 kg for a patient using the following formula:

Dose [ng] / (70 Kg x (100 / % bioavailability)) = net systematically available [ng/kg]

Based on this formula, and the average bioavailability of NOCURNA (0.25%, based on the label), Counterclaimants calculate the dose delivered is about 0.89 ng/kg for the 25 µg dose and about 1.79 ng/kg for the 50 µg dose. [Anticipated testimony of Dr. Mayersohn.]

DFF500. First, using average data for bioavailability is not appropriate in this context because the bioavailability number is a mean, and was shown to be highly variable. It thus has little predictive value for any individual patient. (*See* DFF109-DFF112.) [Anticipated testimony of Dr. Spaans.]

DFF501. Further, even accepting that the use of mean data and Counterclaimants' calculations are appropriate, using the upper and lower values for the 95% confidence interval for bioavailability, it is clear that there are a range of potential values, as shown below:

Bioavailability (%) from confidence interval	25 μg dose	50 μg dose
0.21	0.75 ng/kg	1.5 ng/kg
0.31	1.10 ng/kg	2.20 ng/kg

[Anticipated testimony of Dr. Spaans.]

DFF502. Based on the data in Example 8, doses of 0.5 ng/kg delivered to the bloodstream are insufficient to meet the durations of action claimed in the asserted claims of the '321 patent. [Anticipated testimony of Mr. Vis, Dr. Mayersohn.]

DFF503. Based on the data in Example 8, doses of 1.0 ng/kg delivered to the bloodstream were insufficient to meet the durations of action claimed in the asserted claims of the '321 patent in seven of the eight individuals tested in Example 8. [Anticipated testimony of Mr. Vis, Dr. Mayersohn.]

DFF504. Based on the data in Example 8, doses of 2.0 ng/kg delivered to the bloodstream were in some cases insufficient to meet the durations of action claimed in the asserted claims of the '321 patent and in other cases resulted in durations of action that were too long to meet the durations of action claimed in the asserted claims of the '321 patent. [Anticipated testimony of Mr. Vis, Dr. Mayersohn.]

DFF505. Given the inherent variability in the data, and Counterclaimants' expert's admission that not all doses below 2.0 ng/kg are effective (and indeed, that the doses must be near 2.0 ng/kg), Counterclaimants' calculations are insufficient to show that this limitation is necessarily met.

e) The label is insufficient to show that administration of NOCDURNA to a patient will necessarily infringe the asserted claims

DFF506. The NOCDURNA label does not provide pharmacokinetic data for NOCDURNA. Instead, the label states, "[t]he pharmacokinetics of desmopressin following sublingual administration of NOCDURNA (25 mcg/day and 50 mcg/day desmopressin) has not been characterized. The pharmacokinetic information provided below is from studies following sublingual administration of higher doses or intravenous injection of desmopressin." (JX-5-0009.)

DFF507. There are no plasma concentrations at all reported in the NOCDURNA label. (*See generally*, JX-5.)

DFF508. The NOCDURNA label does not provide any information about reducing the risk of hyponatremia relative to other desmopressin products. (*See generally*, JX-5.)

DFF509. The NOCDURNA label explicitly states that "NOCDURNA is contraindicated in patients at increased risk of severe hyponatremia." (JX-5-0004 at § 5.1.)

DFF510. The NOCDURNA label explicitly states that "[u]se of NOCDURNA without concomitant reduction of fluid intake may lead to fluid retention and hyponatremia." (JX-5-0004 at § 5.1.)

DFF511. The NOCDURNA label, in describing a pharmacodynamic study, states that "the mean time to onset of antidiuretic action was observed within 30 minutes and lasted 6 hours after dosing." (JX-5-0009 at § 12.2.) This statement was made with respect to a dose of desmopressin that the label describes as "1.2 and 2.4 times the maximum recommended dose in men and women, respectively" and that the individuals in the study had "suppression of the

endogenous vasopressin release by continuous intake of water." (JX-5-0009 at § 12.2.) [Anticipated testimony of Dr. Mayersohn, Dr. Spaans, Dr. Juul.]

DFF512. There is no urine osmolality data reported in the NOCDURNA label. (*See generally*, JX-5.)

B. Counterclaimants have not shown that Ferring has the specific intent to induce others to infringe the asserted claims as required under 35 U.S.C. § 271(b) and have not shown that Ferring knows that NOCDURNA is "especially made" or "especially adapted" to infringe the asserted claims as required by 35 U.S.C. § 271(c)

DFF513. As discussed above, the pharmacokinetics and pharmacodynamics of desmopressin formulations typically exhibit a high degree of variability and mean data is not representative of any specific individual within the population. Further, data from healthy individuals (and children) cannot necessarily be extrapolated to patient populations without verification. (DFF109-DFF112; DFF454-DFF456; DFF474-DFF475.) [Anticipated testimony of Dr. Juul, Dr. Spaans.]

1. Given the inherent variability in plasma concentrations after administration of NOCDURNA, it is not possible to identify which patients, if any, will infringe and thus Ferring cannot have the specific intent to induce infringement and cannot have known that NOCDURNA is "especially made" or "especially adapted" to infringe the asserted claims as required by 35 U.S.C. § 271(c)

DFF514. As discussed above, orodispersible tablet formulations of desmopressin have not been shown to be dose linear outside of the tested ranges, and "[t]he pharmacokinetic profile cannot be determined to show that desmopressin melt pharmacokinetics is linear over the dose range of 10, 25, 50, and 100 mcg used in the Phase 3 clinical studies, due to the sensitivity limitations of available validated assays." (PX-22 at FERSER0000014.) (DFF464-DFF469.)

DFF515. As discussed above, Ferring's CS006, CS007A, CS021, and CS030 studies all exhibit a high degree of variability, such that the mean values are not representative of

any specific individual within the population. (DFF109-DFF112; DFF454-DFF456; DFF485-DFF486; DFF496; DFF497.)

DFF516. As discussed above, Counterclaimants do not account for this significant variability in performing their calculations. (DFF471; DFF484-DFF486; DFF494-DFF495; DFF497.)

DFF517. As discussed above, the Canadian monograph relied on by Counterclaimants also indicates the data are highly variable. (DFF472.)

DFF518. As discussed above, the data in Example 7 of the Ferring patents is the same as the data in Example 7 of the common specification and the tablets tested in Example 7 are quantitatively different than the NOCDURNA tablets. (DFF473.)

DFF519. As discussed above, the data relied on by Counterclaimants is in individuals who are not patients (or patients suffering from nocturia), and comes from controlled clinical studies, not the real world. (DFF454-DFF456; DFF474-DFF475; DFF481; DFF493; DFF497.)

DFF520. It is not possible to determine if any particular patient, or even if any patients in a given group, will meet the plasma concentration limitations of the asserted claims based on mean plasma concentration data. (DFF109-DFF112; DFF470-DFF471.) [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

DFF521. Counterclaimants have not shown that a patient will necessarily meet the plasma concentration limitations of the asserted claims following administration of NOCDURNA. (DFF109-DFF112; DFF470-DFF471.)

2. Given the inherent variability in pharmacodynamic response after administration of NOCDURNA, it is not possible to identify which patients, if any, will infringe, and thus Ferring cannot have the specific intent to induce infringement and cannot have known that

NOCDURNA is "especially made" or "especially adapted" to infringe the asserted claims as required by 35 U.S.C. § 271(c)

DFF522. As discussed above, the mean data presented in Ferring's CS021 study are insufficient to show that any particular individual will achieve the durations of action in asserted claim 6 of the '203 patent or the asserted claims of the '321 patent. (DFF480-DFF481.)

DFF523. As discussed above, CS006 does not show that any particular individual patient will achieve the claimed durations of action in asserted claim 6 of the '203 patent or the asserted claims of the '321 patent. (DFF482-DFF489.)

DFF524. As discussed above, Yamaguchi 2012 does not show that any individual patient will achieve the claimed durations of action in asserted claim 6 of the '203 patent or the asserted claims of the '321 patent. (DFF490-DFF491.)

DFF525. As discussed above, CS007A does not show that any individual patient will achieve the claimed durations of action in asserted claim 6 of the '203 patent or the asserted claims of the '321 patent. (DFF493-DFF496.)

DFF526. As discussed above, CS030 does not show that any individual patient will achieve the claimed durations of action in asserted claim 6 of the '203 patent or the asserted claims of the '321 patent. (DFF497.)

DFF527. It is not possible to determine if any particular patient, or even if any patients in a given group, will meet the duration of action limitations of the asserted claims based on mean data. (DFF112; DFF455; DFF474-DFF475.) [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

DFF528. Counterclaimants have not shown that a patient will necessarily meet the duration of action limitations of the asserted claims following administration of NOCDURNA. (DFF109-DFF112; DFF454-DFF456; DFF474-DFF475; DFF497.)

3. Given the inherent variability in NOCDURNA bioavailability, it is not possible to identify which patients, if any, infringe the asserted claims and thus Ferring cannot have the specific intent to induce infringement and cannot have known that NOCDURNA is "especially made" or "especially adapted" to infringe the asserted claims as required by 35 U.S.C. § 271(c)

DFF529. As discussed above, the 95% confidence interval for NOCDURNA's bioavailability is 0.21% to 0.31%. (DFF501.)

DFF530. As discussed above, not all doses below 2.0 ng/kg are effective and not all doses below 2.0 ng/kg will meet the limitations of the asserted claims of the '321 patent. (DFF502-DFF504.)

DFF531. It is not possible to determine if any particular patient, or even if any patients in a given group, will meet the 2.0 ng/kg limitation of the asserted claims of the '321 patent based on mean bioavailability data. (DFF502-DFF504.) [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

DFF532. Counterclaimants have not shown that a patient will necessarily meet the the 2.0 ng/kg limitation of the asserted claims of the '321 patent following administration of NOCDURNA. (DFF502-DFF504.)

4. The label is insufficient to show that Ferring has the required specific intent to induce infringement or that Ferring knows that NOCDURNA is "especially made" or "especially adapted" to infringe the asserted claims as required by 35 U.S.C. § 271(c)

DFF533. As discussed above, the label does not explicitly or inherently teach an individual to administer NOCDURNA in a way that will necessarily infringe the asserted claims of the patents in suit. (DFF506-DFF512.)

DFF534. It is not possible to determine if any particular patient, or even if any patients in a given group, will infringe any of the asserted claims based on the information in the label. (DFF506-DFF512.) [Anticipated testimony of Dr. Spaans, Dr. Mayersohn.]

DFF535. Counterclaimants have not shown that a patient will necessarily infringe any of the asserted claims following administration of NOCDURNA by following the label. (DFF506-DFF512.)

IX. Additional Findings of Fact Regarding Infringement

DFF536. The Court construed "transmucosal," "transmucosal delivery" / "transmucosal . . . delivery," "delivering to the bloodstream . . . by [via] transmucosal . . . administration," and "transmucosal administration" / "administering . . . by transmucosal administration" (collectively, the "transmucosal limitations") which appear in one or more of the asserted claims. (D.I. 421.) Under the Court's construction of the transmucosal limitations, the terms do not require absorption, only administration or delivery to the mucosal tissue. (*See, e.g.*, D.I. 421 at 16 ("Ferring's proposal, that "transmucosal" delivery be defined to necessarily involve "transmucosal absorption" is unsupported by the language of the Common Specification, which decouples the concept of delivery of desmopressin to the mouth from absorption through the mouth."); D.I. 421 at 18 ("'[D]elivery of desmopressin need not involve actual absorption . . . ."); D.I. 421 at 19 ("[T]here is no indication in the specification or elsewhere that Dr. Fein meant for 'transmucosal . . . administration' to be limited definitionally to 'transmucosal absorption.'").)

DFF537. Ferring disagrees with the Court's construction, at least because pharmacologic effects require absorption. However, under the Court's claim construction—which requires no absorption—Ferring does not dispute that the transmucosal limitations of the asserted claims are met. To the extent that the transmucosal limitations are later construed to require at least some transmucosal absorption, Ferring denies that the transmucosal limitations are met.

DFF538. During claim construction, Ferring argued that the independent claims of the patents in suit (and thus by extension the dependent claims) "should be construed as limited to 'a dose of desmopressin in the range of 0.5 ng to no greater than 20 µg.'" (D.I. 198 at 7-19.)

DFF539. In its claim construction order, the Court rejected Ferring's arguments and specifically stated that the claims were not limited to "a dose of desmopressin in the range of 0.5 ng to 20 µg." (D.I. 421 at 22-40.)

DFF540. Counterclaimants' sole infringement argument under the doctrine of equivalents is that "[t]he Nocdurna products (the 25 and 50 mcg equivalents) are insubstantially different than 'a dose of desmopressin in the range of 0.5 ng to no greater than 20 µg.'" [Anticipated testimony of Dr. Mayersohn.]

DFF541. In other words, Counterclaimants' equivalence argument seeks to equate the asserted claims to a claim construction that has been rejected by this Court.

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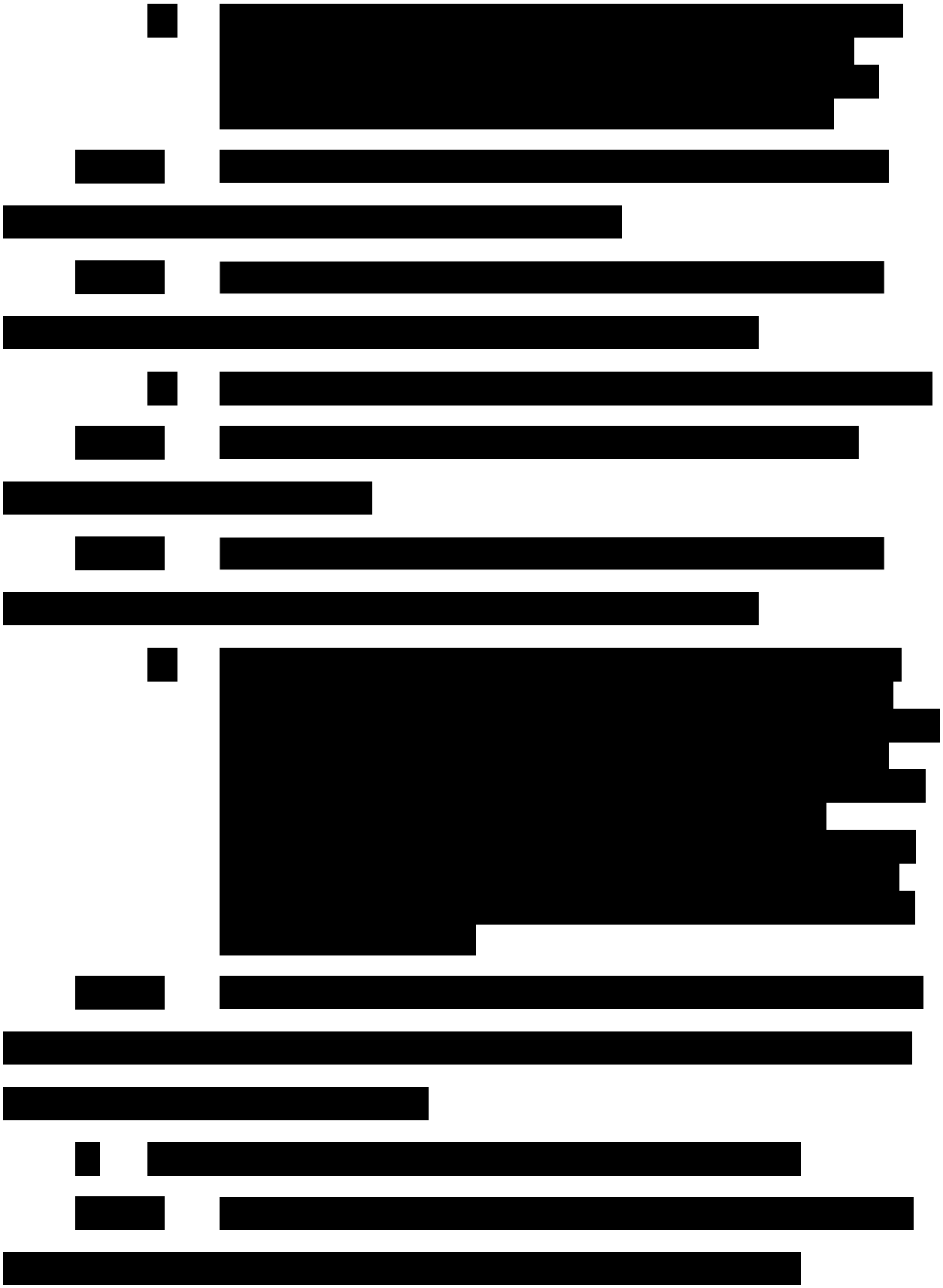

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CONCLUSIONS OF LAW

I. Legal Standards and Principles Governing the Patents in Suit and their Examination

DCL1. The patents in suit are subject to the pre-American Invents Act standards, including those found in Chapter 35 of the United States Code, Chapter 37 of the Code of Federal Regulation ("CFR"), and the MANUAL OF PATENT EXAMINING PROCEDURE, 8th ed. ("MPEP"). *See* MPEP § 2159.01; *see also, In re Portola Packaging*, *Inc.*, 110 F.3d 786, 788 (Fed. Cir. 1997) (stating that the MPEP "does not have the force of law, [but] provides guidance and instructions to examiners").

DCL2. The courts "presume[] that the Patent Office complies with its own [procedural] rules, a presumption overcome only upon presentation of contrary evidence." *Genzyme Corp. v. Transkaryotic Therapies, Inc.*, 346 F.3d 1094, 1103 (Fed. Cir. 2003); *see also In re NTP, Inc.*, 654 F.3d 1268, 1279 (Fed. Cir. 2011) ("[a]s Congress acknowledged, examiners have limited time to review each application and cannot be expected to fully address every possible issue before them") (*citing* H.R. Rep. 107-120 (June 28, 2001)).

DCL3. The presumption of validity under 35 U.S.C. § 282 is a rebuttable presumption. *See, e.g., Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1352 (Fed. Cir. 2013); *Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1259–61 (Fed. Cir. 2012) (vacating and remanding to the district court based on patent challenger raising a "substantial question of validity"); *see also Cleveland Clinic Found. v. True Health Diagnostics LLC*, 760 F. App'x 1013, 1021 (Fed. Cir. 2019) (noting that "deference" "to the examiner's decision to allow the asserted claims" "is incorporated into the presumption of patent validity," and affirming the district court's dismissal of infringement claims by finding asserted claims invalid).

DCL4. Moreover, in context of 35 U.S.C. § 112, "[a]ny deference due to a Patent Examiner" may be overcome by "clear and convincing evidence that the specification does not support the asserted claims" of the patents in suit. *Purdue Pharma L.P. v. Faulding Inc.,* 230 F.3d 1320, 1329 (Fed. Cir. 2000); *see also In re NTP, Inc.*, 654 F.3d at 1279 (Fed. Cir. 2011) (finding that the examiner did not consider whether a continuation patent's specification complied with § 112).

II. The Asserted Claims Are Invalid for Lack of Written Description under 35 U.S.C. § 112, ¶ 1

A. Legal standard

DCL5. "The specification shall contain a written description of the invention." 35 U.S.C. § 112, ¶ 1.

DCL6. The written description requirement "plays a vital role in curtailing claims . . . that have not been invented, and thus cannot be described." *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1299 (Fed. Cir. 2014) (citing *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1352 (Fed. Cir. 2010)).

DCL7. As such, the "purpose of the written description requirement is to ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification." *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 920 (Fed. Cir. 2004) (internal quotation omitted).

DCL8. Compliance with the written description requirement is a "fact-based inquiry" that necessarily varies "depending on the nature of the invention claimed." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 963 (Fed. Cir. 2002) (citation omitted).

DCL9. Pursuant to the written description requirement, the applicant must "convey with reasonable clarity to those skilled in the art, as of the filing date sought, he or she was in possession of the invention. The invention is, for the purposes of the 'written description' inquiry, whatever is now claimed." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991) (emphasis omitted).

DCL10. Assessing "possession as shown in the disclosure requires an objective inquiry into the four corners of the specification." *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1348 (Fed. Cir. 2011) (citation omitted); *see also Idenix Pharm. LLC v. Gilead*

Scis. Inc., 941 F.3d 1149, 1161 (Fed. Cir. 2019) ("a patent owner must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and *demonstrate that by disclosure in the specification of the patent*" (emphasis added; internal quotation omitted)).

DCL11. "The written description requirement often becomes an issue in cases in which a broad genus is claimed and the specification discloses only one or a few species of that genus." *Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F. Supp. 3d 566, 618 (D. Del. 2018), *aff'd on other grounds*, *Persion Pharm. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184 (Fed. Cir. 2019).

DCL12. The problem presented by generic claims "is especially acute with genus claims that use functional language to define the boundaries of the claimed genus." *Ariad*, 598 F.3d at 1349.

DCL13. For such claims—genus claims that define the boundaries of the genus with functional language—to have adequate written description support, the specification must disclose "either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Id.* at 1350 (quoting *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568-69 (Fed. Cir. 1997)).

DCL14. "A 'mere wish or plan' for obtaining the claimed invention is not adequate written description." *Centocor*, 636 F.3d 1341, 1348 (Fed. Cir. 2011) (quoting *Regents*, 119 F.3d at 1566).

DCL15. The written description requirement is "not a question of whether one skilled in the art *might* be able to construct the patentee's device from the teachings of the

disclosure. . . . Rather, it is a question whether the application necessarily discloses that particular device." *PowerOasis, Inc. v. T-Mobile USA, Inc*., 522 F.3d 1299, 1306 (Fed. Cir. 2008) (citing *Martin v. Mayer*, 823 F.2d 500, 505 (Fed. Cir. 1987)).

DCL16. For example, "[s]election of [a disease] from a list of diseases and selection of [a dosage] from a large range of possible dosages" involves "necessary picking and choosing to arrive at the claimed invention" and "does not indicate it was described." *FWP IP ApS v. Biogen MA., Inc*., 749 F. App'x 969, 973 (Fed. Cir. 2018). Rather, Federal Circuit "case law requires the specification itself to provide the blaze marks necessary to guide a skilled artisan to the claimed invention." *Id*.

DCL17. Also for example, for claims directed to routes of administration of a drug, if little was known by the skilled artisan at the time of filing about administering the drug by those routes of administration or formulating the drug for administration by those means, and the specification reports only general information—e.g., that the methods comprise administering an "effective amount" by the claimed routes of administration, that the drug may be administered alone or in combination with other excipients, that dosages will be determined by the administering physician—the inventors' belief that scientists could practice the claimed invention is insufficient to satisfy the written description requirement. *Wyeth v. Abbott Labs*., 2012 WL 175023, at *9-10 (D.N.J. Jan. 19, 2012) (granting summary judgment of invalidity for insufficient written description and lack of enablement), *aff'd on other grounds*, 720 F.3d 1380 (Fed. Cir. 2013) (affirming invalidity for lack of enablement).

B. The asserted claims are invalid for lack of written description under the standards set forth by Judge Bryson in *Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F. Supp. 3d 566 (D. Del. 2018)

DCL18. The asserted claims are defined by functional limitations. (DFF113-DFF115.)

DCL19. The asserted claims cover treatment with nearly any desmopressin formulation as long as the functional limitations of the claims are met. (DFF117, DFF121-DFF125, DFF132.)

DCL20. Accordingly, the asserted claims are invalid for lack of written description because they inadequately describe the genus of formulations used in the claimed methods. (DFF113-DFF126.)

C. The asserted claims of the ’203 patent and claims 6 and 7 of the ’321 patent are invalid for lack of written description because there is no support for the claimed plasma concentration ranges

DCL21. The asserted claims of the ’203 patent and claims 6 and 7 of the ’321 patent each claim a broad range of plasma concentration ranges. (DFF135-DFF147.)

DCL22. However, the Examples in the common specification do not teach formulations or methods of treatment that fall within the claimed plasma concentration ranges. (DFF142-DFF147.)

DCL23. Asserted claim 6 of the ’203 patent is invalid for lack for written description because the claimed plasma concentration range is not explicitly disclosed in the common specification. (DFF145.)

DCL24. The asserted claims of the ’203 patent and claims 6 and 7 of the ’321 patent are invalid for lack of written description because there is no support for the claimed plasma concentration ranges. (DFF135-DFF157.)

D. The asserted claimed of the ’321 patent and asserted claim 6 of the ’203 patent are invalid for lack of written description because there is no support for the claimed durations of antidiuretic effect

DCL25. Example 8 in the common specification set forth an explicit methodology for calculating the duration of action as a function of urine osmolality over time. (DFF169-DFF175.)

DCL26. When the duration of action is calculated based on the explicit methodology set forth in Example 8, the durations of action do not support a duration of action of between about four to six hours, as required by the asserted claims. (DFF176-DFF181.)

DCL27. The urine osmolality data in Example 8 also does not support a duration of action of less than about five hours after administration for urine osmolalities ranging above about 300 mOsm/kg. (DFF182-DFF183.)

DCL28. Accordingly, the asserted claims of the ’321 patent and asserted claim 6 of the ’203 patent are invalid for lack of written description because there is no support for the claimed durations of antidiuretic effect. (DFF158-DFF183.)

E. Asserted claim 12 of the ’321 patent is invalid for lack of written description because there is no support for the “300 mOsm/kg” limitation

DCL29. The 300 mOsm/kg limitation recited in claim 12, as it depends from claim 8, is not explicitly disclosed in the common specification. (DFF186-DFF187.)

DCL30. Accordingly, asserted claim 12 of the ’321 patent is invalid for lack of written description because there is no support for the “300 mOsm/kg” limitation. (DFF186-DFF187.)

F. The asserted claims are invalid for lack of written description because there is no support for the claimed methods

DCL31. The common specification fails to disclose a specific dose or dose range that, when used in any dosage forms and routes of administration covered by the asserted claims, would achieve the claimed therapeutic effects and other recited properties (e.g., blood plasma concentrations) and, therefore, the common specification does not provide a practicing physician with enough information to recognize what is part of the invention. (DFF188-DFF190.)

DCL32. The common specification fails to demonstrate that Dr. Fein was in possession of the methods for achieving the recited therapeutic effects for all of the dosage forms and routes of administration covered by the claims. The disclosure does not allow persons of ordinary skill in the art to recognize that Dr. Fein invented the claimed methods. (DFF192-DFF193.)

DCL33. The asserted claims are invalid for lack of written description because there is inadequate support for the claimed methods of treatment. (DFF188-DFF190; DFF192-DFF193.)

G. The asserted claims of the '321 patent are invalid for lack of written description because there is no support for the claimed reduction of the risk of hyponatremia

DCL34. The common specification does not provide a sufficient disclosure regarding the claimed methods for reducing the risk of hyponatremia. Serum sodium data would be the minimum disclosure needed by a POSITA to evaluate whether there was a risk of hyponatremia. And even more would be needed to show that Dr. Fein actually invented—was in possession of—a method for reducing such a risk while still practicing the claimed methods (of achieving therapeutic efficacy via treating various voiding disorders, inducing voiding postponement, or inducing an antidiuretic effect), particularly with seemingly limitless

combinations of dosage forms, routes of administration, and doses provided in the common specification. (DFF195-DFF197.)

DCL35. Accordingly, the asserted claims of the ’321 patent are invalid for lack of written description because there is no support for the claimed reduction of the risk of hyponatremia. (DFF195-DFF207.)

III. The Asserted Claims Are Invalid for Lack of Enablement under 35 U.S.C. § 112, ¶ 1

A. Legal standards

DCL36. "The specification shall [also] contain . . . the manner and process of making and using [the claimed invention], in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same." 35 U.S.C. § 112, ¶ 1.

DCL37. The enablement requirement is separate and distinct from the written description requirement. *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351-52 (Fed. Cir. 2009).

DCL38. "Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed." *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371 (Fed. Cir. 1999) (citation omitted).

DCL39. "The enablement requirement ensures that the public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims. The scope of the claims must be less than or equal to the scope of the enablement. The scope of enablement, in turn, is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation." *Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.,* 166 F.3d 1190, 1195-96 (Fed. Cir. 1999).

DCL40. Therefore, "a patentee chooses broad claim language at the peril of losing any claim that cannot be enabled across its full scope of coverage." *MagSil Corp. v. Hitachi Global Storage Techs., Inc.*, 687 F.3d 1377, 1381 (Fed. Cir. 2012).

DCL41. Courts may consider several factors "in determining whether a disclosure would require undue experimentation," including: "(1) the quantity of experimentation

necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

DCL42. "It is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement." *Idenix Pharm. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1159 (Fed. Cir. 2019) (quoting *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997)).

DCL43. "A specification that requires a [POSITA] to 'engage in an iterative, trial-and-error process to practice the claimed invention' does not provide an enabling disclosure." *Idenix*, 941 F.3d at 1159 (Fed. Cir. 2019) (quoting *ALZA Corp. v. Andrx Pharm., LLC*, 603 F.3d 935, 941 (Fed. Cir. 2010)).

DCL44. "Tossing out the mere germ of an idea does not constitute enabling disclosure." *Genentech*, 108 F.3d at 1366; *see also ALZA*, 603 F.3d at 939-43 (reasoning that the enablement requirement is not met when the specification provides "only a starting point, a direction for further research").

DCL45. "If mere plausibility were the test for enablement under section 112, applicants could obtain rights to 'inventions' consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the 'inventor' would be rewarded with the spoils instead of the party who demonstrated the method actually worked." *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1325 (Fed. Cir. 2005).

DCL46. "Simply observing that [a POSITA could make and use the invention]—years after the patent's effective filing date—bears little on the enablement inquiry." *Trustees of Boston Univ. v. Everlight Elecs. Co*., 896 F.3d 1357, 1364 (Fed. Cir. 2018).

DCL47. "The deficiencies in the description as to enablement cannot be cured in [every] case by looking to the knowledge of those skilled in the art at the time of the invention." *Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc*., 928 F.3d 1340, 1348 (Fed. Cir. 2019) (finding an example listed in the specification to be "insufficient" as a working example because it lacked any "bench experiment" demonstrating *functionality* as per the claims).

DCL48. Further, it is improper to fill gaps in the supporting disclosure with the knowledge of POSITA, because doing so is "an impermissible end-run around the requirement to enable the full scope of the claim." *Idenix*, 941 F.3d at 1159.

DCL49. If there is no known method and no specific guidance in the specification on how a drug could be administered by a particular route of administration to be effective in treating a disease particularly in a "poorly understood field," claims listing this and other routes of administration may not be enabled. *Wyeth v. Abbott Labs*., 720 F.3d 1380, 1384-86 (Fed. Cir. 2013).

B. The asserted claims are invalid for lack of enablement under the standards set forth in by Judge Bryson in *Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F. Supp. 3d 566 (D. Del. 2018)

DCL50. The asserted claims are defined by functional limitations. (DFF113-DFF115.)

DCL51. The asserted claims cover treatment with nearly any desmopressin formulation as long as the functional limitations of the claims are met. (DFF117; DFF121-DFF125; DFF132.)

DCL52. Making and using desmopressin formulations that actually fall within the claimed genus of formulations would require undue experimentation. (DFF127-DFF134.)

DCL53. Accordingly, the asserted claims invalid for lack of enablement under the standards set forth in by Judge Bryson in *Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F. Supp. 3d 566 (D. Del. 2018). (DFF113-DFF115; DFF1177; DFF121-125; DFF127-DFF134.)

C. The asserted claims of the ’321 patent and asserted claim 6 of the ’203 patent are invalid for lack of enablement because there is no support for the claimed durations of action

DCL54. Example 8 in the common specification sets forth an explicit methodology for calculating the duration of action as a function of urine osmolality over time. (DFF169-DFF175.)

DCL55. When the duration of action is calculated based on the explicit methodology set forth in Example 8, the durations of action do not support a duration of action of between about four to six hours, as required by the asserted claims. (DFF176-DFF181.)

DCL56. The urine osmolality data in Example 8 also does not support a duration of action of less than about five hours after administration for urine osmolalities ranging above about 300 mOsm/kg. (DFF182-DFF183.)

DCL57. In view of the faulty guidance in the specification, determining how to treat a patient to achieve the claimed durations of action would require undue experimentation. (DFF184-DFF185.)

DCL58. Accordingly, the asserted claims of the ’321 patent and asserted claim 6 of the ’203 patent are invalid for lack of enablement because there is no support for the claimed durations of antidiuretic effect. (DFF169-DFF185.)

D. The asserted claims are invalid for lack of enablement because there is no support for the claimed methods

DCL59. The common specification fails to disclose a specific dose or dose range that applies to all dosage forms and routes of administration covered by the asserted claims and, therefore, the common specification does not provide a practicing physician with enough information to know which dosage forms and routes of administration would achieve the claimed therapeutic effects and other recited properties (*e.g.*, blood plasma concentrations), and which do not. (DFF188-DFF192.)

DCL60. Determining how to treat a patient for the recited conditions using the claimed methods would require undue experimentation. (DFF194.)

DCL61. Accordingly, the asserted claims are invalid for lack of enablement because there is no support for the claimed methods. (DFF188-DFF192; DFF194.)

E. The asserted claims are invalid for lack of enablement based on Dr. Fein's admissions in front of the EPO

DCL62. Admissions by a patent applicant regarding the validity of their prior art patents may render them invalid. *See Funai Elec. Co. v. Orion Elec. Co.*, No. 01-cv-3501 (AGS)(JCF), 2002 WL 1808419, at *2 (S.D.N.Y. Aug. 7, 2002) ("Actions and statements against interest of the owner of a patent or inventor may be considered by a court when construing the scope of a patent and are relevant to the issues of infringement and validity." (internal quotation omitted)); *Components, Inc. v. W. Elec. Co.*, 52 F.R.D. 379, 382 (D. Me. 1971) ("It appears to be settled law [by 1971] that the actions and statements against interest of the inventor or owner of a patent may properly be considered by the Court in construing the scope of the patent, and are therefore relevant to the issues of validity and infringement." (citing, inter alia, *Jungersen v. Baden*, 166 F.2d 807, 809 (2d Cir. 1948), *aff'd*, 335 U.S. 560 (1949))); *see also Fiers v. Revel*,

984 F.2d 1164, 1171 (Fed. Cir. 1993) (in the context of a written description analysis, affirming finding that a patent applicant's testimony that he or she did not possess the claimed subject matter is evidence that the description is inadequate).

DCL63. Under PTO rules, practices, and procedures, admissions by applicants in an application or during the prosecution of an application are considered by the PTO and may be relied on in evaluating patentability. The CFR states:

> In rejecting claims the examiner may rely upon admissions by the applicant, or the patent owner in a reexamination proceeding, as to any matter affecting patentability and, insofar as rejections in applications are concerned, may also rely upon facts within his or her knowledge pursuant to paragraph (d) (2) of this section.

37 CFR § 1.104(c)(3). Thus, applicant admissions made during the prosecution of a patent before the PTO may inform and affect the scope and validity of the claims of a patent issuing therefrom.

DCL64. Under PTO practices and procedures, prior art references must meet the enablement requirement of 35 U.S.C. § 112, first paragraph. The PTO presumes that a prior art reference is enabled. However, an applicant may argue that a prior art reference is not enabled and if successful, the teaching of that prior art is eliminated such that it cannot be used as a basis for rejection. This practice has been explained by the Federal Circuit and adopted into the MPEP: "[t]he disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation." *Elan Pharm., Inc. v. Mayo Found. for Med. Educ. & Res.*, 346 F.3d 1051, 1055 (Fed. Cir. 2003); *see also* MPEP (8th ed., rev. 2) § 2121.01. The same reasoning applies in the context of prior art references relied upon in the context of an obviousness rejection.

DCL65. Even admissions by an applicant before the EPO regarding the validity of their prior art United States patents may render them invalid. *See, e.g., Tanabe Seiyaku Co., Ltd. v. USITC,* 109 F.3d 726, 733 (Fed. Cir. 1997); *Sarazin v. Wright Aeronautical Corp.*, 54 F. Supp. 244, 251 (S.D.N.Y. 1944), *aff'd sub nom., Clark v. Wright Aeronautical Corp.*, 162 F.2d 960 (2d Cir. 1947) (holding a patentee's appraisal of his own invention made during prosecution of corresponding foreign patent applications constituted "admissions against interest" and finding the claims were not enabled).

DCL66. Dr. Fein's statements before the EPO regarding the sufficiency of the disclosure in the common specification (i.e., the specification of the '203 patent, referred to as D8 before the EPO during the opposition proceeding for the Eur '821 patent) to support the patentability of the claims constitute admissions against his interest in the validity of the patents in suit. (DFF208-DFF217.)

DCL67. Dr. Fein's admissions before the EPO are evidence that the common specification does not enable one of ordinary skill in the art to make and use the inventions claimed in the patents in suit. (DFF208-DFF217.)

DCL68. Accordingly, Dr. Fein's admissions before the EPO that the common specification does not enable one of ordinary skill in the art to make and use the inventions claimed in the patents in suit render the asserted claims not enabled and invalid. (DFF208-DFF217.)

F. Asserted claims 10, 11, 12, and 13 of the '203 patent are invalid for lack of enablement for the "amount" of desmopressin and the "time sufficient to achieve" the claimed plasma concentrations

DCL69. There are no restrictions on the "amount" of desmopressin that may be administered in asserted claims 10, 11, 12, and 13 of the '203 patent. A person of ordinary skill in the art would be faced with a myriad of different potential formulations. (DFF219-DFF225.)

DCL70. It is undisputed that the common specification provides no guidance for the "time sufficient to achieve" the plasma concentrations claimed in asserted claims 10, 11, 12, and 13 of the '203 patent. (DFF226.)

DCL71. A POSITA would not be able to determine the "amount" of desmopressin and how it should be administered for a "time sufficient to achieve" the required plasma concentrations without undue experimentation. (DFF227-DFF229.)

DCL72. Accordingly, asserted claims 10, 11, 12, and 13 of the '203 patent are not enabled for the "amount" of desmopressin and the "time sufficient to achieve" the claimed plasma concentrations. (DFF219-DF229.)

G. The asserted claims of the '321 patent are invalid for lack of enablement for the "no more than about 2 ng/kg" limitation

DCL73. Based on the disclosures in Example 8 of the common specification, it is undisputed that some doses of desmopressin that deliver "no more than about 2 ng/kg" of desmopressin to the bloodstream will not meet the requirements of the asserted claims of the '321 patent. (DFF233-DFF235; DFF241-DFF242.)

DCL74. The asserted claims of the '321 patent are broad and cover treatment with a myriad of formulations that can be administered by five different routes of administration. (DFF239.)

DCL75. The data in the Examples and elsewhere in the common specification are insufficient to extrapolate to other formulations to achieve the claimed durations of action. (DFF236-DFF238.)

DCL76. Based on the disclosures in Example 8 of the common specification, a POSITA would not know what amount below 2 ng/kg desmopressin must be delivered to a patient's bloodstream to meet the limitations of the claim. (DFF242-DFF243.)

DCL77. Practicing the methods claimed in the asserted claims of the '321 patent would require undue experimentation. (DFF244.)

DCL78. Accordingly, the asserted claims of the '321 patent are not enabled for the "no more than about 2 ng/kg" limitation. (DFF230-DFF244.)

IV. The Asserted Claims of the '321 Patent Are Indefinite under 35 U.S.C. § 112, ¶ 2

DCL79. The claims of a patent must "particularly point[] out and distinctly claim[] the subject matter which the applicant regards as his invention." 35 U.S.C. § 112, ¶ 2. Patent claims which fail to do so, are indefinite.

DCL80. Patent claims are invalid as indefinite if, "read in light of the specification delineating the patent, and the prosecution history, [the claims] fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014).

DCL81. While patent claims may use terms of degree, "a term of degree that is purely subjective and depends on the unpredictable vagaries of any one person's opinion is indefinite." *Intellectual Ventures I LLC v. T-Mobile USA, Inc.*, 902 F.3d 1372, 1381 (Fed. Cir. 2018) (internal quotations omitted); *see, also, Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1218 (Fed. Cir. 1991) (affirming the district court's finding that "nothing in the specification, prosecution history, or prior art provides any indication as to what range of specific activity is covered by the term 'about,' and by the fact that no expert testified as to a definite meaning for the term in the context of the prior art").

DCL82. Counterclaimants' expert Dr. Mayersohn has admitted that he does not know the scope of what is encompassed in the "about" term based on the common specification. (DFF249-DFF250.)

DCL83. Because Counterclaimants' own expert cannot determine the scope of the term "about," asserted claims 6 and 12 of the '203 patent and the asserted claims of the '321 patent are. (DFF249-DFF250.)

V. If the Court Adopts Dr. Mayersohn's Assumptions Underlying His Infringement Opinions, Claims 10, 11, 12, and 13 of the '203 Patent Are Obvious under 35 U.S.C. § 103

DCL84. "A patent for a claimed invention may not be obtained . . . if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103.

DCL85. In determining obviousness, "an invention must be considered as a whole, . . . and claims must be considered in their entirety." *Medtronic, Inc. v. Cardiac Pacemakers, Inc.*, 721 F.2d 1563, 1567 (Fed. Cir. 1983) (internal quotations omitted).

DCL86. Courts evaluate several factors to determine whether an establishment of obviousness is warranted. Pursuant to § 103, "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved." *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17 (1966).

DCL87. A property such as a pharmacokinetic parameter, when claimed as a limitation, is inherent if it is necessarily present in the prior art combination. *See Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1369 (Fed. Cir. 2012) (finding inherency appropriate in obviousness context where it concerns a "property that is necessarily present"); *see also Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) ("[A]n obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations. To hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property."); *In re Kubin*, 561 F.3d 1351, 1357 (Fed. Cir. 2009) ("Even if no prior art of record explicitly discusses

the [limitation], the . . . application itself instructs that [the limitation] is not an additional requirement imposed by the claims on the [claimed invention], but rather a property necessarily present in the [claimed invention].").

DCL88. "[A] suggestion, teaching, or motivation to combine the relevant prior art teachings to achieve the claimed invention does not have to be found explicitly in the prior art references sought to be combined, but rather 'may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself.'" *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1362 (Fed. Cir. 2007) (citing *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1361 (Fed. Cir. 2006)).

DCL89. "Probative of the required level of skill in the art are factors such as educational level of the inventor, educational level of those who work in the industry [in] which [the art sits], and the sophistication of technology involved." *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991).

DCL90. "[E]vidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness." *Stratoflex. Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983). "Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Graham*, 383 U.S. at 17.

DCL91. Although the weight attributed to each factor may differ, the analysis of all available factors "continue[s] to define the inquiry that controls" the rendering of patents and claims thereof obvious. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 407 (2007).

DCL92. Evidence of secondary considerations must be probative of a finding of nonobviousness, however. For example, "[a]bsent a showing of long-felt need or the failure of others, the mere passage of time without the claimed invention is not evidence of nonobviousness." *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004).

DCL93. Asserted claims 10, 11, 12, and 13 of the '203 patent are obvious in view of the Ferring 1998 Label in combination with the Finnish 2001 Label and Fjellestad-Paulsen (1993) if the Court adopts Dr. Mayersohn's assumptions regarding linearity. (DFF251-DFF286.)

DCL94. The asserted secondary indicia are insufficient to overcome the finding of obviousness. (DFF287-DFF288.)

VI. The Patents in Suit Are Invalid under 35 U.S.C. § 102(f) Because Dr. Fein Himself Did Not Invent the Subject Matter Sought to be Patented

A. Dr. Nørgaard and Dr. Senderovitz, not Dr. Fein, are the inventors of the subject matter claimed in the patents in suit, and the patents in suit are therefore invalid

DCL95. An applicant is not entitled to a patent if "he did not himself invent the subject matter sought to be patented" 35 U.S.C. § 102(f).

DCL96. A patent must accurately name the correct inventors of a claimed invention. *Pannu v. Iolab Corp.*, 155 F.3d 1344, 1349 (Fed. Cir. 1998).

DCL97. A patent is invalid "if more or fewer than the true inventors are named." *Gemstar-TV Guide Int'l v. USITC*, 383 F.3d 1352, 1381 (Fed. Cir. 2004).

DCL98. Demonstrating that a patent claim is invalid under section 102(f) because the named inventor derived the claimed invention from another requires proof of "both prior conception of the invention by another and communication of that conception to the patentee." *Eaton Corp. v. Rockwell Int'l Corp.*, 323 F.3d 1332, 1344 (Fed. Cir. 2003); *Cumberland Pharm. Inc. v. Mylan Institutional LLC*, 846 F.3d 1213, 1218 (Fed. Cir. 2017) (citation omitted).

DCL99. "[A]n inventorship analysis, like an infringement or invalidity analysis, begins as a first step with a construction of each asserted claim to determine the subject matter encompassed thereby. The second step is then to compare the alleged contributions of each asserted co-inventor with the subject matter of the properly construed claim to then determine whether the correct inventors were named." *Trovan, Ltd. v. Sokymat SA, Irori*, 299 F.3d 1292, 1302 (Fed. Cir. 2002).

1. Conception

DCL100. "Conception is the formation in the mind of the inventor of a definite and permanent idea of the complete and operative invention, as it is therefore to be applied in

practice" and "must encompass all limitations of the claimed invention." *Singh v. Brake*, 317 F.3d 1334, 1340 (Fed. Cir. 2003) (internal quotations and citation omitted).

2. Collaboration

DCL101. Joint inventorship requires clear and convincing proof of collaboration. "[T]here must be some element of joint behavior, such as collaboration or working under common direction." *Kimberly-Clark Corp. v. Proctor & Gamble Distrib. Co.*, 973 F.2d 911, 917 (Fed. Cir. 1992).

3. Corroboration

DCL102. The law also requires "corroborating evidence of a contemporaneous disclosure that would enable one of ordinary skill in the art to make the invention." *Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 1461 (Fed. Cir. 1994). Corroboration is determined under a "rule of reason" analysis, evaluating "all pertinent evidence." *Ethicon, Inc. v. U.S. Surgical Corp.*, 135 F.3d 1456, 1461 (Fed. Cir. 1998).

DCL103. An individual's testimony regarding their own inventorship "cannot, standing alone, rise to the level of clear and convincing proof." *Symantec Corp. v. Comp. Assocs. Int'l, Inc.*, 522 F.3d 1279, 1295 (Fed. Cir. 2008).

DCL104. "Documentary or physical evidence that is made contemporaneously with the inventive process provides the most reliable proof" of corroboration. *Trovan*, 299 F.3d at 1302.

DCL105. To the extent the Court does not find the asserted claims of the patents in suit invalid for lack of written description, enablement, indefiniteness, or obviousness, the claims of the patents in suit are invalid under 35 U.S.C. § 102(f) because Dr. Fein derived the claimed subject matter from Dr. Nørgaard and Dr. Senderovitz. (DFF289-DFF407.) Dr. Nørgaard and Dr.

Senderovitz conceived of the claimed subject matter and communicated that conception to Dr. Fein. (DFF334-DFF407.)

B. Dr. Nørgaard and Dr. Senderovitz are at the very least co-inventors of the subject matter claimed in the patents in suit, and Ferring therefore cannot infringe the patents in suit

DCL106. "When an invention is made by two or more persons jointly, they shall apply for patent jointly and each make the required oath." 35 U.S.C. § 116.

DCL107. A joint inventor must "(1) contribute in some significant manner to the conception or reduction to practice of the invention, (2) make a contribution to the [conception of] the claimed invention that is not insignificant in quality, when that contribution is measured against the dimension of the full invention, and (3) do more than merely explain to the real inventors well-known concepts and/or the current state of the art." *Pannu*, 155 F.3d at 1351.

DCL108. Because "[c]onception is the touchstone of inventorship," each joint inventor must contribute to the conception of the invention. *Burroughs,* 40 F.3d at 1227-28.

DCL109. Joint inventorship arises only "when collaboration or concerted effort occurs" such that a joint inventor "must demonstrate that his labors were conjoined with the efforts of the named inventors." *Eli Lilly & Co. v. Aradigm Corp.*, 376 F.3d 1352, 1359 (Fed. Cir. 2004).

DCL110. Alternatively, to the extent the Court does not find the asserted claims of the patents in suit invalid for lack of written description, enablement, indefiniteness, or obviousness, the claims of the patents in suit are invalid for failure to name Dr. Nørgaard and Dr. Senderovitz as joint inventors. (DFF289-DFF407.)

VII. The Patents in Suit Are Unenforceable Due to Inequitable Conduct

DCL111. Applications for patents are required to include an inventor's oath or declaration from each inventor. *See* 37 CFR § 1.51.

DCL112. An application must name all inventors who contributed to the conception of the claimed invention. The question of inventorship is determined by the claims of the application or patent. *See Trovan, Ltd. v. Sokymat SA, Irori*, 299 F.3d 1292, 1302 (Fed. Cir. 2002); *see also* MPEP § 2137.01.

DCL113. Statements made in an oath or declaration by inventors are sworn statements made under the penalty of perjury. *See* MPEP § 602. The PTO assumes that the statements made in the oath or declaration are truthful and that the inventors have reviewed the contents of the application and understand the significance of the statements made. *See* 37 CFR §§ 1.56 & 1.63.

DCL114. Patent applicants "have a duty to prosecute patent applications in the [PTO] with candor, good faith, and honesty." *Honeywell Int'l Inc. v. Universal Avionics Sys. Corp.,* 488 F.3d 982, 999 (Fed. Cir. 2007); *see also* 37 C.F.R. § 1.56(a) (2009) ("Rule 56").

DCL115. The "duty of candor and good faith" mandates "disclosure where the information establishes either 'a prima facie case of unpatentability' or 'refutes, or is inconsistent with a position the applicant takes' such that this "duty of candor and good faith" "is broader than the duty to disclose material information." *Dayco Prod., Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1363-64 (Fed. Cir. 2003) *quoting* 37 C.F.R. § 1.56(b).

DCL116. The "duty of candor and good faith" applies to all submissions to the PTO by an applicant because the examiners routinely take applicant argument "at face value." *See, e.g.,* MPEP § 2304.02(c)(I); *see, also*, MPEP § 2107.

DCL117. "Inequitable conduct is an equitable defense to patent infringement that, if proved, bars enforcement of the patent." *Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1285 (Fed. Cir. 2011).

DCL118. A party asserting inequitable conduct must prove by clear and convincing evidence that "the applicant misrepresented or omitted material information with the specific intent to deceive the PTO." *Id.* at 1287.

DCL119. "Intent and materiality are separate requirements." *Id.* at 1290; *see also Praxair, Inc. v. ATMI, Inc.,* 543 F.3d 1306, 1313 (Fed. Cir. 2008).

DCL120. "[A]s a general matter, the materiality required to establish inequitable conduct is but-for materiality." *Therasense*, 649 F.3d at 1291.

DCL121. "Materiality is not limited to prior art but embraces *any* information that a reasonable examiner would be substantially likely to consider important in deciding whether to allow an application to issue as a patent." MPEP § 2001.04 *(*quoting *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, 326 F.3d 1226, 1234 (Fed. Cir. 2003)) (emphasis in original).

DCL122. "Although but-for materiality generally must be proved to satisfy the materiality prong of inequitable conduct, [there is] an exception in cases of affirmative egregious misconduct." *Therasense*, 649 F.3d at 1292.

DCL123. Affirmative acts of egregious misconduct, "such as the filing of an unmistakably false affidavit," are material. *Id.* at 1292.

DCL124. Under the intent prong, a party can prove intent to deceive the PTO based on direct evidence or on circumstantial evidence. *Id.* at 1290-91; *see also Merck & Co., Inc. v. Danbury Pharmacal, Inc.,* 873 F.2d 1418, 1422 (Fed. Cir. 1989) ("Intent need not, and rarely can, be proven by direct evidence.").

DCL125. Intent to deceive "must be the single most reasonable inference able to be drawn from the evidence'" "to meet the clear and convincing standard." *Therasense*, 649 F.3d at 1290 (quoting *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.,* 537 F.3d 1357, 1366 (Fed. Cir. 2008)).

DCL126. Submission of a false affidavit raises a strong inference of intent to deceive. *See Intellect Wireless, Inc. v. HTC Corp*., 732 F.3d 1339, 1345 (Fed. Cir. 2013) ("Submission of an affidavit containing fabricated examples of actual reduction to practice in order to overcome a prior art reference raises a strong inference of intent to deceive") (citing *Rohm & Haas Co. v. Crystal Chem. Co.*, 722 F.2d 1556, 1571 (Fed. Cir. 1983)).

DCL127. The claim of sole inventorship in Dr. Fein's Combined Declaration is unmistakably false. (*See* DFF439.)

DCL128. The false claim of sole inventorship in Dr. Fein's Combined Declaration is material to the patentability of the patents in suit.

DCL129. Dr. Fein's submission of his false Combined Declaration during prosecution of the '100 application and both patents in suit was an egregious affirmative misrepresentation. (*See* DFF442.)

DCL130. The most reasonable inference to be drawn from Dr. Fein's submission of his false Combined Declaration during prosecution of the '100 application and both patents in suit was that it was submitted with the intent to deceive the PTO. (*See* DFF443.)

DCL131. Dr. Fein's submission of his false Combined Declaration during prosecution of the '100 application and both patents in suit constituted inequitable conduct.

DCL132. The patents in suit are unenforceable due to Dr. Fein's inequitable conduct during prosecution of the patents in suit. (DFF408-DFF443.)

VIII. Infringement - Generally

DCL133. Counterclaimants must prove by a preponderance of the evidence that Ferring infringes the asserted method claims either directly or indirectly. *Cross Medical Prods, Inc. v. Medtronic Sofamor Danek, Inc.*, 424 F.3d 1293, 1310 (Fed. Cir. 2005).

DCL134. The infringement analysis involves two steps: the first step (an issue of law) is to construe the asserted claims and the second step (an issue of fact) is to compare the properly construed claims to the allegedly infringing method or product. *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 384-85 (1996); *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1581-82 (Fed. Cir. 1996).

DCL135. The Court issued its claim construction order on January 22, 2019 (D.I. 421), completing the first step in the infringement analysis.

DCL136. The second step of the infringement analysis shows that Ferring does not infringe, either directly or indirectly, any of the asserted claims.

IX. Ferring Does Not Directly Infringe the Asserted Claims under 35 U.S.C. § 271(a)

DCL137. Section 271(a) provides that, "[e]xcept as otherwise provided in this title, whoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefor, infringes the patent." 35 U.S.C. § 271(a).

DCL138. To prove direct infringement under 35 U.S.C. § 271(a), Counterclaimants must prove by a preponderance of the evidence that the accused method of treatment "embodies every limitation of the [asserted] claim[s], either literally or by an equivalent." *Carroll Touch, Inc. v. Electro Mech. Sys., Inc.*, 15 F.3d 1573, 1576 (Fed. Cir. 1993).

DCL139. In the context of method claims, such a "claim is *directly* infringed only by one practicing the patented method." *Joy Techs., Inc. v. Flakt, Inc.,* 6 F.3d 770, 775 (Fed. Cir. 1993) (emphasis in original)); *see also Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311 (Fed. Cir. 2006) ("Method claims are only infringed when the claimed process is performed, not by the sale of an apparatus that is capable of infringing use."). There can be no liability under 35 U.S.C. §271(a) for direct infringement of a method claim where the accused infringer does not itself perform the steps set forth in the asserted claims. *See, e.g., Ormco*, 463 F.3d at 1311; *Joy Techs.,* 6 F.3d at 775.

DCL140. To prove direct infringement by Ferring under 35 U.S.C. § 271(a), Counterclaimants must show that Ferring administers its NOCDURNA products to a patient in accordance with the claims. *See, e.g., Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1363 (Fed. Cir. 2003); *Akamai Techs., Inc. v. Limelight Networks, Inc.*, 797 F.3d 1020, 1022 (Fed. Cir. 2015).

DCL141. But drug manufacturers generally are not liable for direct infringement of method claims requiring administration of drugs or treatment of patients. *See Warner-Lambert*, 316 F.3d at 1363; *see also Endo Pharm. Inc. v. Amneal Pharm., LLC*, No. 12-cv-8060 (TPG), 2015 WL 9459823, at *29 (S.D.N.Y., Aug. 18, 2015) (holding that a drug manufacturer did not directly infringe the claimed methods because they "do not feed tablets to patients or subjects, and thus do not 'administer' them" as required by the claims), *amended in part*, 2016 WL 1732751 (S.D.N.Y. Apr. 29, 2016).

DCL142. In *Warner-Lambert*, the Federal Circuit noted that there was "no evidence in the record that [the accused drug manufacturer] had directly practiced or will ever practice any of the methods claimed" and, therefore, there was no direct infringement by the accused drug manufacturer. *Warner-Lambert*, 316 F.3d at 1363. The court further noted that

> pharmaceutical companies do not generally treat diseases; rather, they sell drugs to wholesalers or pharmacists, who in turn sell the drugs to patients possessing prescriptions from physicians. Pharmaceutical companies also occasionally give samples of drugs to doctors and hospitals. In none of these cases, however, does the company itself *treat* the disease.

Id. at 1363 n.7.

DCL143. Here, Counterclaimants have put forth no evidence that Ferring itself has practiced any of the asserted methods of treatment. (DFF444-DFF445.)

DCL144. Counterclaimants also have put forth no evidence that Ferring employs or otherwise has an agency relationship with any individual who has practiced any of the asserted methods of treatment. (DFF446.)

DCL145. Counterclaimants have failed to prove that Ferring directly infringes any of the asserted claims. (DFF444-DFF446.)

X. Ferring Does Not Indirectly Infringe the Asserted Claims Under 35 U.S.C. §§ 271(b) or (c)

DCL146. "To prevail under a theory of indirect infringement, [the patentee] must first prove that the defendants' actions led to direct infringement." *Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc.*, 843 F.3d 1315, 1331 (Fed. Cir. 2016) (quoting *Dynacore Holdings Corp. v. U.S. Philips Corp.*, 363 F.3d 1263, 1274 (Fed. Cir. 2004)). Therefore, here, Counterclaimants must show that someone such as a healthcare provider or patient directly infringes (i.e., administers NOCDURNA in accordance with the claims) within the terms of 35 U.S.C. § 271(a). *See, e.g., Limelight Networks, Inc. v. Akamai Techs., Inc.*, 572 U.S. 915, 920-2 (2014); *see also Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1363 (Fed. Cir. 2003).

DCL147. Unlike in Hatch-Waxman litigation under 35 U.S.C. 271 where the infringement of an ANDA product is hypothetical, *see Warner-Lambert*, 316 F.3d at 1365-66, in cases where a product is on the market, such as this one, "[h]ypothetical instances of direct infringement are insufficient to establish . . . indirect infringement" *ACCO Brands, Inc. v. ABA Locks Mfrs.*, 501 F.3d 1307, 1313 (Fed. Cir. 2007) (citing *Dynacore*, 363 F.3d at 1274).

DCL148. Thus, Counterclaimants "must either point to specific instances of direct infringement or show that the accused device necessarily infringes the patent in suit." *ACCO*, 501 F.3d at 1313 (citing *Dynacore*, 363 F.3d at 1275-76 (Fed. Cir. 2004)); *see also Piersons v. Quality Archery Designs, Inc.*, No. 3:06-cv-0408 (TJM/DEP), 2009 WL 10680314, at *32 (N.D.N.Y., Feb. 26, 2009) ("where infringement does not necessarily occur in every instance, [it] is insufficient as a predicate basis to find indirect infringement") (citing *Ball Aerosol & Specialty Container, Inc. v. Ltd. Brands, Inc.*, 555 F.3d 984 (Fed. Cir. 2009))..

DCL149. In *ACCO Brands*, the Federal Circuit stated that the patentee "failed to point to specific instances of direct infringement," noting that:

> [t]he sole witness at trial who testified to having used the lock in an infringing manner was [the patentee's] expert . . . . However, the record contains no evidence of actual users having operated the lock in an infringing manner. [The patentee] proffered no witness testimony of actual [accused infringer] key lock users, or surveys of [the accused infringer's] customers, that would indicate that a user, aside from the expert retained for this particular litigation, directly infringed the [patent in suit].

ACCO, 501 F.3d at 1313.

DCL150. The *ACCO Brands* Court further stated that:

> the parties do not dispute that the accused device can be operated in either of two modes—the infringing Dornfeld method or the noninfringing press-to-lock method. Because the accused device can be used at any given time in a noninfringing manner, the accused device does not necessarily infringe the [patent in suit].

Id.

DCL151. Here, Counterclaimants have failed to show a single instance of direct infringement of any of the asserted claims with Ferring's NOCDURNA product by anyone. (DFF447-DFF453.)

DCL152. Counterclaimants have failed to show that the use of NOCDURNA necessarily infringes any of the asserted claims. (DFF457-DFF512.)

DCL153. Therefore, Counterclaimants have failed to prove indirect infringement, either under 35 U.S.C. §§ 271(b) or (c), because they have not shown direct infringement of any of the asserted claims.

A. Ferring does not induce infringement of any asserted claim

DCL154. To prove induced infringement, a patentee must satisfy three requirements: (i) that there has been direct infringement of the asserted method claims; (ii) the accused inducing party had knowledge of the asserted patents and that the induced acts constitute patent infringement; and (iii) the accused inducing party had the specific intent to encourage

another's infringement. *See, e.g.*, *Commil USA, LLC v. Cisco Sys., Inc.*, 135 S.Ct. 1920, 1926 (2015); *Akamai*, 572 U.S. at 921; *DSU Med. Corp. v. JMS Co.,* 471 F.3d 1293, 1305 (Fed. Cir. 2006). Inducement also "requires successful communication between the alleged inducer and the third-party direct infringer." *Power Integrations*, 843 F.3d at 1331.

DCL155. As explained above (DCL146-DCL153), Counterclaimants have failed to provide evidence of direct infringement so cannot prove that Ferring is liable for induced infringement.

DCL156. With an accused drug product on the market, whether the drug manufacturer has "induce[d] someone to infringe can only be determined *when that act occurs*." *Warner-Lambert*, 316 F.3d at 1365 (emphasis added); *see also ACCO*, 501 F.3d at 1313.

DCL157. In such a case where a drug is on the market, the District of Delaware has reasoned that to provide specific intent to support a finding of inducement, "reliance on a label and speculation about what may occur in the future cannot substitute for *actual evidence* about what has *actually occurred* in the past when, as in this case, there has been a period of actual, past conduct that is pertinent to infringement." *GlaxoSmithKline LLC v. Teva Pharms. USA, Inc.*, 313 F.Supp.3d 582, 596 n.14 (D. Del. 2018) (emphasis added), *appeal docketed*, No. 18-1976 (May 16, 2018), *cross appeal docketed*, No. 18-2023 (May 31, 2018). The Delaware court rejected the argument that "the marketing of a generic drug with labeling that encourages infringement can be viewed as causing infringement" in the case where the drug is actually on the market, reasoning that "GSK's inducement claims are not premised on a hypothetical, but instead must be supported by sufficient evidence as to what actually happened in the relevant time period [when actual, past conduct pertinent to infringement occurred]." *GlaxoSmithKline*, 313 F.Supp.3d at 596 n.14 (emphasis added).

DCL158. Counterclaimants "must [] establish[] that the defendant possessed specific intent to encourage another's infringement and not merely that the defendant had knowledge of the acts alleged to constitute inducement." *DSU*, 471 F.3d at 1306 (en banc in relevant part) (internal quotation and citation omitted); *see also Power Integrations*, 843 F.3d at 1330, 1332 (vacating trial court's verdict after an erroneous jury instruction that "[direct] infringement need not have been actually caused by the [alleged inducer]'s actions").

DCL159. To the extent that Counterclaimants rely on the NOCDURNA label to show that Ferring possessed the specific intent to encourage infringement, Counterclaimants have not proven that the NOCDURNA label instructs users to administer the drug by the claimed method, such that *all* the functional limitations of the asserted claims are *necessarily* met. *See, e.g., Takeda Pharm., U.S.A., Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015).

DCL160. A "scholarly scavenger hunt through the label to identify statements that may *inferentially but not inevitably* tie a physician's thoughts or acts … necessarily fails" as a method of proving inducement. *Otsuka Pharm. Co. v. Torrent Pharm. Ltd.*, 99 F. Supp. 3d 461, 493 (D.N.J. 2015) (emphasis added) (internal quotation marks omitted); *Acorda Therapeutics Inc. v. Apotex Inc.,* No. 07-cv-4937 (GEB-M), 2011 WL 4074116, at *20 (D.N.J. Sept. 6, 2011) (finding no specific intent because "[t]he label does not direct infringement, and while the information might allow people to infringe, the ultimate question is not whether some physicians may infringe the patent"), *aff'd*, 476 F. App'x 746 (Fed. Cir. 2012).

DCL161. Knowledge of possible infringement is not enough; where a product has substantial noninfringing uses, such as where there is a high degree of variability, intent to

induce infringement cannot be inferred. *See Acorda*, 2011 WL 4074116, at *20 (D.N.J. Sept. 6, 2011).

DCL162. Counterclaimants' reliance on the NOCDURNA label cannot support a finding of intent to induce the functional limitations of the asserted claims. The NOCDURNA label does not provide any pharmacokinetic data. (DFF506-DFF507.) Therefore, the NOCDURNA label is insufficient to show that administration of NOCDURNA to a patient will necessarily infringe the asserted claims and Ferring cannot have the required intent to induce infringement. (DFF506-DFF512.)

DCL163. Counterclaimants have not established the threshold requirement of direct infringement(either by specific instances of direct infringement or that the accused method necessarily infringes) and, therefore, have failed to show that Ferring has induced infringement under 35 U.S.C. § 271(b). (DCL146-DCL153.)

DCL164. And even if Counterclaimants had established the threshold requirement of direct infringement, Counterclaimants have failed to show that Ferring has the specific intent to induce infringement as required under 35 U.S.C. § 271(b). (DFF513-535.)

DCL165. Therefore, Counterclaimants have failed to prove by a preponderance of the evidence that Ferring induces infringement of any of the asserted claims under 35 U.S.C. § 271(b).

B. Ferring does not contributorily infringe any asserted claim under 35 U.S.C. § 271(c)

DCL166. To prove contributory infringement, a patentee must prove by a preponderance of the evidence that the defendant "offers to sell or sells within the United States or imports into the United States a component of a patented machine, manufacture, combination or composition, or a material or apparatus for use in practicing a patented process, constituting a

material part of the invention, knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial noninfringing use." 35 U.S.C. § 271(c).

DCL167. As an initial matter, "[i]t is plain that § 271(c) [] made no change in the fundamental precept that there can be no contributory infringement in the absence of a direct infringement." *Aro Mfg. Co. v. Convertible Top Replacement Co.*, 365 U.S. 336, 341 (1961).

DCL168. Here, Counterclaimants must show, in addition to an underlying act of direct infringement by another (such as a healthcare provider or patient), that: (i) NOCDURNA is being used as a material element in an infringing method, (ii) Ferring had knowledge that NOCDURNA is especially made or especially adapted for use in infringing the claimed methods, and (iii) NOCDURNA is not a staple item of commerce suitable for substantial non-infringing use. *See, e.g., Fujitsu Ltd. v. Netgear Inc.*, 620 F.3d 1321, 1326 (Fed. Cir. 2010); *C.R. Bard*, *Inc. v. Advanced Cardiovascular Sys.*, 911 F.2d 670, 673 (Fed. Cir. 1990).

DCL169. With respect to the knowledge required to establish contributory infringement, a patentee must show that the accused infringer "knew that the combination for which its components were especially made was both patented and infringing." *Fujitsu*, 620 F.3d at 1330 (internal quotation and citations omitted). Here, that requires Counterclaimants to show that NOCDURNA was especially made *such that it infringes* the asserted claims (i.e., that it meets the functional limitations of the claimed methods).

DCL170. Even instructions that teach customers each step of the claimed method can be insufficient to show the necessary knowledge to support a finding of contributory infringement in the absence of evidence of actual evidence of infringement by a user. *See E-Pass Techs., Inc. v. 3Com Corp.*, 473 F.3d 1213, 1221-23 (Fed. Cir. 2007).

DCL171. In *E-Pass Techs.*, the Federal Circuit held that the district court properly granted summary judgment of no infringement where the evidence showed that the accused devices could be used for a variety of purposes and in a variety of ways and did not show that anyone actually did practice the claimed methods. *E-Pass Techs.*, 473 F.3d at 1222-23 (Fed. Cir. 2007). Specifically, the Court found that

> [T]he evidence here shows, at best, that the Palm defendants taught their customers each step of the claimed method in isolation. Nowhere do the manual excerpts teach all of the steps of the claimed method together, much less in the required order. Accordingly, *it requires too speculative a leap to conclude that any customer actually performed the claimed method*. Indeed, the very same record evidence upon which E-Pass attempts to rely also shows that the accused PDAs are general-purpose computing devices that can be used for a variety of purposes and in a variety of ways. . . . *If, as E-Pass argues, it is 'unfathomable' that no user in possession of one of the accused devices and its manual has practiced the accused method, E-Pass should have had no difficulty in meeting its burden of proof and in introducing testimony of even one such user*. Having failed to meet that burden, E-Pass has no basis to overturn the district court's decision.

Id. (emphasis added) (internal quotation and citations omitted).

DCL172. Counterclaimants have not established the threshold requirement of direct infringement (either by specific instances of direct infringement or that the accused method necessarily infringes) and, therefore, have failed to show that Ferring contributorily infringes under 35 U.S.C. § 271(c). (DCL146-DCL153.)

DCL173. Even if Counterclaimants had established the threshold requirement of direct infringement, Counterclaimants have failed to show that Ferring had knowledge that NOCDURNA is especially made or especially adapted for use in infringing any of the asserted claimed methods because it does not necessarily infringe the asserted claims. (*See* DFF513-DFF535.)

DCL174. Counterclaimants have failed to prove by a preponderance of the evidence that Ferring contributorily infringed any of the asserted claims under 35 U.S.C. § 271(c).

XI. Counterclaimants Are Not Entitled to the Damages and/or Injunctive Relief Sought, Even if the Patents in Suit Are Found to Be Valid, Enforceable, and Infringed

A. Legal standards and principles governing Serenity's and Reprise's request for damages

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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[redacted]

XII. Even if the Court Determines that The Patents in Suit Are Valid, Enforceable, and Infringed, Counterclaimants Cannot Demonstrate that Infringement on Behalf of Ferring Is Willful, or that Enhanced Damages or Attorneys' Fees Are Appropriate

DCL229. In certain cases where an accused infringer's conduct is found to be willful, "the court may increase the damages up to three times the amount found or assessed." 35 U.S.C. § 284. However, as described by the Supreme Court, "[a]wards of enhanced damages under the Patent Act over the past 180 years establish that they are not to be meted out in a typical infringement case, but are instead designed as a 'punitive' or 'vindictive' sanction for egregious infringement behavior. The sort of conduct warranting enhanced damages has been variously described in our cases as willful, wanton, malicious, bad-faith, deliberate, consciously wrongful, flagrant, or—indeed—characteristic of a pirate." *Halo Elecs., Inc. v. Pulse Elecs., Inc*., 136 S. Ct. 1923, 1932 (2016); *Presidio Components, Inc. v. Am. Tech. Ceramics Corp*., 875 F.3d 1369, 1382 (Fed. Cir. 2017) ("Enhanced damages are generally only appropriate in egregious cases of misconduct, such as willful, wanton, or malicious behavior."). No such circumstances exist in this case.

DCL230. "Discretion remains with the court to determine whether the conduct is sufficiently egregious to warrant enhanced damages." *Presidio*, 875 F.3d at 1382. However, "the channel of review ha[s] narrowed" in light of "nearly two centuries of discretionary awards and review by appellate tribunals." *Halo*, 136 S. Ct. at 1932 (internal quotation marks and citations omitted).

DCL231. Additionally, although "[e]nhanced damages are generally only appropriate in egregious cases of misconduct, such as willful, wanton, or malicious behavior[,] . . . an award of enhanced damages does not necessarily flow from a willfulness finding." *Presidio*,

875 F.3d at 1382; *see also Halo*, 136 S. Ct. at 1933 ("[N]one of this is to say that enhanced damages must follow a finding of egregious misconduct.")

DCL232. "In determining whether enhanced damages are appropriate, courts should consider the overall circumstances of the case." *Presidio*, 875 F.3d at 1382. In "garden variety" patent infringement cases—where the accused infringer maintains colorable noninfringement and/or invalidity defenses—enhanced damages generally are not appropriate even in those instances in which it is determined that infringement is willful. *Id.* (upholding district court's denial of enhanced damages where jury determined that infringement was willful because in light of colorable defenses and conduct, "the district court concluded that the present case was a 'garden-variety' hard-fought patent case, rather than an egregious case of misconduct"); *Halo*, 136 S. Ct. at 1935 ("That balance can indeed be disrupted if enhanced damages are awarded in garden-variety cases.")

DCL233. In *Halo*, the Supreme Court determined that the Federal Circuit's test for willful infringement was overly restrictive, and specified that "[t]he subjective willfulness of a patent infringer, intentional or knowing, may warrant enhanced damaged damages, without regard to whether his infringement was objectively reckless." *Halo*, 136 S. Ct. at 1933. This articulation of the test for willfulness was a rejection of the two-part test for willfulness adopted by the Federal Circuit, in which the *Halo* court took exception to the ability of a purposeful infringer to avoid a finding of willful infringement by "muster[ing] a reasonable (even if unsuccessful) defense at the infringement trial" "even if he did not act on the basis of the defense or was even aware of it." *Id.*

DCL234. Ferring has always maintained that the patents in suit do not claim any patentable subject matter. From the time of the Speranza-Barclay correspondence, Ferring has

maintained that the subject matter of Dr. Fein's patents was already known in the art or was otherwise not patentable. (D.I. 143, Ex. B at AGN_FER000002772 (noting that by at least April 2003, Ferring had determined that Dr. Fein's alleged inventive contribution—"the low dosage possibilities enabled by the sublingual administration route"—were at that time "already available in the prior art").) Ferring has also consistently maintained that to the extent the patents in suit are construed and/or otherwise contain any patentable subject matter, Dr. Fein is not the proper named inventor of that subject matter because the subject matter was derived from the work of other Ferring scientists. Thus, Ferring has maintained a good faith belief that the patents in suit are invalid and/or could not be asserted against Ferring since well before any accused infringement began.

DCL235. Ferring launched NOCDURNA on November 9, 2018. (DFF79.) On November 8, 2018, this Court denied Counterclaimants' motion for a preliminary injunction. (D.I. 300.) In denying Counterclaimants' bid for a preliminary injunction, the Court specifically found that Ferring had raised substantial questions regarding whether the use of NOCDURNA would infringe any asserted claim of the patents in suit and noted (but did not address) that Ferring had also raised defenses based on the invalidity and unenforceability of those claims. (*See id.*) These findings—entered by the Court before any alleged infringement by Ferring—preclude a finding of willful infringement.

DCL236. Counterclaimants' allegations with respect to willful infringement and enhancement of damages reference only Ferring's non-infringement positions. Ferring disagrees that its noninfringement positions are meritless, and notes that the fact that Counterclaimants have failed to show even a single act of actual infringement more than a year after the launch of NOCDURNA further underscores the strength of its positions. Regardless, Ferring also notes

that Counterclaimants' demand for enhanced damages fails to consider Ferring's invalidity defenses, which must be considered as part of the totality of the circumstances approach delineated by the Supreme Court in *Halo*.

DCL237. Further, even if the Court were to determine that Ferring's infringement was willful, the totality of the circumstances does not justify the enhancement of damages at this stage. Similarly, Ferring's conduct of this case, including its maintenance of meritorious noninfringement and invalidity defenses, does not justify a finding that this case is "exceptional" under 35 U.S.C. § 285. To the extent that Counterclaimants suggest an award of attorneys' fees is appropriate separate and apart from a determination that a case is "exceptional" under § 285 that is contrary to the law. *See Octane Fitness, LLC v. ICON Health & Fitness, Inc.*, 572 U.S. 545, 553 (2014) ("Our analysis begins and ends with the text of § 285: 'The court in exceptional cases may award reasonable attorney fees to the prevailing party.'")

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Of Counsel:

Mary W. Bourke
Kristen Healey Cramer
Dana K. Severance
Daniel M. Attaway
Nicholas T. Verna
WOMBLE BOND DICKINSON (US) LLP
1313 North Market Street, Suite 1200
Wilmington, DE 19801
Telephone: (302) 252-4320
Mary.Bourke@wbd-us.com
Kristen.Cramer@wbd-us.com
Dana.Severance@wbd-us.com
Daniel.Attaway@wbd-us.com
Nick.Verna@wbd-us.com

John W. Cox
WOMBLE BOND DICKINSON (US) LLP
271 17th Street NW, Suite 2400
Atlanta, GA 30363
Telephone: (404)-872-7000
John.Cox@wbd-us.com

Joshua P. Davis
WOMBLE BOND DICKINSON (US), LLP
811 Main Street
Suite 3130
Houston, TX 77002
Telephone: (346) 998-7801
Joshua.P.Davis@wbd-us.com

Kenneth Mueller
John B. Bourke
WOMBLE BOND DICKINSON (US) LLP
Independence Wharf
470 Atlantic Avenue
Suite 600
Boston, MA 02210
Telephone: (857) 287-3133
Kenneth.Mueller@wbd-us.com
Ben.Bourke@wbd-us.com

GIBBONS P.C.

s/ William P. Deni, Jr.
William P. Deni, Jr.
One Gateway Center
Newark, NJ 07102-5310
Telephone: (973) 596-4853
wdeni@gibbonslaw.com

Attorneys for Plaintiffs/ Counterclaim-Defendants